L-PYRROLIDINE-2-CARBOXYLIC ACID SULFATE (LPCAS): A NEW IONIC LIQUID FOR THE SYNTHESIS OF 1,8-DIOXOOCTAHYDROXANTHENES

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Keywords: 1,8-dioxooctahydroxanthenes, L-pyrrolidine-2-carboxylic acid sulfate (LPCAS), eco-friendly, solvent free, ionic liqud

A clean, simple, highly efficient and eco-friendly benign method for the synthesis of 1, 8-dioxooctahydroxanthene derivatives utilizing novel bronsted acidic ionic liquid; L-Pyrrolidine-2-carboxylic acid sulfate (LPCAS) as reagent been reported. Distinguishing features of the methodology are excellent yield of products in shorter reaction time, cleaner reaction profile, environmentally friendly nature and the use of inexpensive reagent.

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Introduction

Organic synthesis commonly includes the use of variety of solvents which are mostly harmful to the environment and human being. Multistep reactions for the synthesis of organic compounds multiply consuming of solvents and reagents, which generates a demand to design and develop environmentally benign multi-component and solvent-free green organic transformations.

Multicomponent reactions (MCR) are processes, in which three or more reactants are combined in one pot to produce products that incorporate substantial portion of all the components; naturally comply with many of these stringent requirements for ideal organic synthesis.

Xanthene derivatives have been attracted various researchers due to significant value in pharmaceutical aspect. 1,8-dioxooctahydroxanthene derivatives have different biological potential as such antibacterial,[1] antiviral[2] and anti-inflammatory,[3] etc. 1,8-dioxo-octahydroxanthene derivatives have medicinal significance. The basic scaffold of these heterocycles could be an attractive model for the identification of new and potential anticancer agents.[4] Literature survey also shows that such derivatives have activities concern with antiplasmodial,[5] antagonists for drug resistant leukemia lines,[6] pH-sensitive fluorescent materials,[7] laser technologies,[8] etc. These compounds are also used as precursors in the synthesis of various organic compounds and dyes.[9,10]

Numerous methods have been reported for efficient and facile synthesis of 1,8-dioxooctahydroxanthenes by using different catalyst, including DBSA.[11] cellulose sulfonic acid.[12] $CaCl_2$,[13] $[Et_3NH][HSO_4]$,[14] $SiCl_4$,[15] ceric ammonium nitrate (CAN),[16] Amberlyst-15,[17] nano-TiO_2,[18] Fe-Montmorillonite,[19] $SmCl_3$,[20] trimethylsilyl chloride,[21] $H_3PW_{12}O_{40}$-MCM-41,[22][bmim]HSO_4,[23] CAN supported on HY-zeolite,[24] [Hbim]BF_4.[25]

These reported methods have various disadvantages and to overcome these problems, we have developed a green protocol for efficient synthesis of 1,8-dioxoocta-hydroxanthenes using a Brönsted acidic ionic liquid, L-pyrrolidine-2-carboxylic acid sulphate LPCAS)[26] Scheme1). Ionic liquids (ILs) are environmental friendly reaction media or catalysts with many excellent advantages such as negligible volatility and good thermal stability.

In the present work, L-pyrrolidine-2-carboxylic acid sulfate as environmentally benign component has been used for the first time in the synthesis of bioactive1,8-dioxo-octahydroxanthene derivatives via multicomponent reaction of aldehydes and dimedone under solvent free conditions (Scheme1).

Experimental Procedure

All the reagents were purchased from Aldrich/Merck and used without further purification. Melting points were obtained 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 silica gel as stationary phase and hexane/ethyl acetate 8:2 as eluent. The products were characterized by comparing melting points and spectral data with authentic melting points and spectroscopic data (IR, ^{1}H NMR). IR spectra were recorded on schimadzu IR Solution 150SUI spectrophotometer using KBr pellet; values are expressed in cm^{-1}. NMR spectra were recorded on Bruker 400 MHz spectrometer using appropriate solvent and TMS as an internal standard. Chemical shift were expressed in ppm.

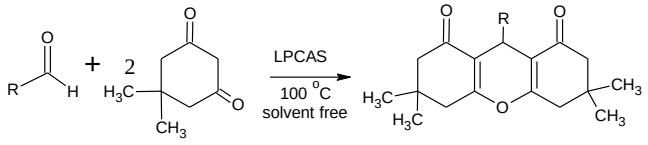
Table 1. Synthesis of 1,8-dioxooctahydroxanthenederivatives catalyzed by LPCAS (3a-j).

Sr. No.	Aldehyde	Time (mins)	Yield (%)	Melting Point (°C) Observed	Reported	References
3a	Benzaldehyde	05	95	202-204	205-206	[27]
3b	4-Nitro bennzaldehyde	10	95	220-222	221-223	[12]
3c	4-hydroxy benzaldehyde	25	85	240-242	241-243	[12]
3d	4-chloro benzaldehyde	05	85	232-234	231-233	[27]
3e	4-Methoxy benzaldehyde	05	95	238-240	241-243	[12]
3f	1-Naphthaldehyde	15	85	230-232	231-233	[16]
3g	4-Dimethylamino benzaldehyde	15	92	220-222	224-226	[11]
3h	2-hydroxy-1-naphthaldehyde	60	85	256-257	--------	This Work
3i	9-Anthraldehyde	50	85	280	---------	This Work
3j	4-Hydroxy-3-methoxy benzaldehyde	55	90	222-224	226-228	[28]

Mass spectra were scanned on a Jeol JMSD-300 spectrometer.

General procedure for synthesisof 1,8-dioxooctahydro-xanthenederivatives

To a mixture of the appropriate aldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (2 mmol) and L-pyrrolidine-2-carboxylic acid sulfate (LPCAS) (1 mmol) was added and the mixture was stirred at 100˚C for appropriate time (Scheme 1). 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. Separated solid was filtered and the crude was recrystallized from ethanol to give the pure product. Similarly the other derivatives were also prepared using same procedure and reported in Table 1.



1a-1j **2** **3(a-j)**

Scheme1. Synthesis of 1,8-dioxooctahydroxanthenederivatives.

Spectral data of selected compounds

The known compounds 3a-g and 3j were identified comparing their physical and spectroscopical data with the reference data.11,12,16,27,28

Compound 3h: FTIR (KBr) (cm 1):3420, 3180, 3056, 2941, 2891, 1643, 1622, 1583, 1373, 1359, 1261, 1234, 1197, 1028, 1010, 746. ^{1}H NMR (400 MHz, DMSO): δ ppm 0.80 (s 3H), 0.92 (s 3H), 0.99 (s 3H), 1.08 (s 3H), 2.06-2.10 (d 2H), 2.27-2.31 (d 2H), 2.38-2.42 (d 2H), 2.51-2.63 (d 2H), 3.39 (brs 1H), 7.18-7.20 (d 1H), 7.35-7.43 (m 2H), 7.71-7.73 (d 1H), 7.79-7.81 (d 1H), 8.19-8.21 (brs 1H), 5.57 (s 1H). ^{13}C NMR (400 MHz, DMSO): 195.80, 147.98, 131.56, 130.47, 128.07, 127.53, 126.23, 117.31, 116.59, 110.68, 50.60, 40.53, 31.67, 31.37, 29.34, 27.55, 25.93. m/z: 417.2.

Compound 3i:FTIR (KBr) (cm ^{1}): 3320, 3130,2986, 2887, 2870, 1661, 1573, 1469, 1371, 1229, 1147, 1014, 1109, 1031,863,732.^{1}H NMR (400 MHz, DMSO): δ ppm 0.85 (s 3H), 0.97 (s 3H), 1.05 (s 3H), 1.29 (s 3H), 2.16-2.21 (m 2H), 2.25-2.31 (m 2H), 2.33-2.46 (m 2H), 2.58-2.66 (m 2H), 4.52 (s 1H), 7.30-7.46 (m 2H), 7.48-7.69 (m 2H), 7.78-7.88 (m 1H), 8.0-8.12 (dd1H), 8.45-8.51 (dd 1H), 8.86 (d 1H), 8.99-9.01 (d 1H). ^{13}C NMR (400 MHz, DMSO): 196.92, 162.90, 135.28, 134.51, 131.46, 131.24, 130.72, 129.34, 129.05, 128.76, 128.44, 128.02,126.75,126.02, 125.83, 125.49, 125.06, 124.95, 124.63, 124.35, 124.19, 123.99, 123.44, 114.31, 111.99, 111.30, 110.07. m/z: 450.21.

Result and discussions

To determine suitable conditions for this transformation, a mixture of benzaldehyde (1 mmol), 5,5-dimethyl-1,3-cyclohexanedione (2 mmol) and LPCAS (1mmol) was added to 25 ml round bottom flask and stirred at 100^{0}C under solvent free conditions.The progress of reaction was monitored by TLC.After completion of reaction, the mixture was cooled to room temperature and 10 ml water was added. Separated solid was filtered, recrystallized product was characterized by IR, ^{1}H and ^{13}C-NMR and Mass spectra.

The efficiency of IL media has been determined and compared with those of reported acid catalysts/reagents in the synthesis of 3,3,6,6-tetramethyl-9-(4-phenyl)-1,8-dioxo-octahydroxanthene (**3a**). The comparison of various reported reagent is summarized in (Table2).

In presence of $[Et_3NH][HSO_4]$, the reaction proceeds at 100 °C within 30 minutes offering 92% yield of the product under solvent free condition (entry 3, Table 2). In presence of *β*-CD-BSA in water the reaction mixture on heating for 15 minutes afforded 95 % of product (entry 1, Table 2). Also by using sonochemical synthesis method in the presence of catalyst $[Hbim]BF_4$ in methanol at 25-30 °C within 45 minutes (entry 14, Table 2).

Similarly in presence of L-proline in dichloromethane at 60 °C, the same reaction proceeds in 360 minutes offering 78 % of product (entry 18, Table 2). Whereas, in presence of $[bmim]ClO_4$ the reaction proceeds at 100 °C within 40 minutes offering 92% yield of the product under solvent free condition (entry 19, Table 2).

Table 2. Comparison of the present catalytic system with some reported protocols in the model reaction between benzaldehyde and dimedone.

Entry	Aldehyde	Conditions	Time	Yield(%)	Ref.
1	*β*-CD-BSA	H_2O	15	95	[29]
2	DBSA	H_2O/100°C	360	94	[11]
3	$[Et_3NH][HSO_4]$	Solvent free/100 °C	30	92	[14]
4	Cellulose sulfonic acid	Solvent free/110 °C	300	95	[12]
5	MCM-41-SO_3H	H_2O/90°C	60	50	[22]
6	$HClO_4$-SiO_2	H_2O/100°C	60	68	[32]
7	Amberlyst-15	CH_3CN/reflux	300	94	[17]
8	Trimethyl silyl chloride	CH_3CN/reflux	480	72	[30]
9	Fe^{3+}-montmorillonite	EtOH/100°C	360	93	[19]
10	CAN supported HY-zeolite	Solvent free/80 °C	45	93	[24]
11	Fe_3O_4@SiO_2-imid-PMA	EtOH/reflux	75	94	[21]
12	Nano-TiO_2	Solvent free/100 °C	15	96	[18]
13	$CaCl_2$	DMSO/90°C	300	87	[13]
14	$[Hbim]BF_4$	Methanol/ ultrasonic irradiation	45	85	[25]
15	$[HBim]HSO_4$	Solvent free /reflux	210	76	[23]
16	Tetrachloro silane	Dichloromethane/60-70 °C	180	92	[15]
17	$SmCl_3$	Solvent free/120 °C	480	98	[20]
18	L-Proline	$ClCH_2CH_2Cl$/60°C	360	78	[31]
19	$[bmim]ClO_4$	Solvent free/100 °C	40	92	[33]
20	L-Pyrrolidine-2-carboxylic acid sulfate(LPCAS)	Solvent free/100 °C	5	95	This work

But surprisingly when the reaction is carried out using ionic liquid L-pyrollidine-2-carboxylic acid sulfate at 100 °C under solvent free condition, it proceeds within 5 minutes and offering the product in 95 % (entry 20, Table 2).

All the above results have showed that, the L-pyrollidine-2-carboxylic acid sulfate 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 by spectroscopic data (IR, ^1H NMR). An advantage of the novel ionic liquid (L-pyrrolidine-2-carboxylic acid sulfate) is; its cost and more efficiency as compare to other reported ionic liquids.

Conclusions

In summary, we have developed a new eco-friendly procedure for the synthesis of 1, 8-dioxo-octahydroxanthenes via one pot condensation of aromatic aryl aldehydes and dimedone using LPCAS as a ionic liquid reagent under solvent free conditions. The hopeful points for the presented methodology are including a simple procedure, high catalytic activity, short reaction time, excellent yields. This approach therefore represents a precious addition to the existing processes for the synthesis of 1, 8-dioxo-octahydro xanthenes.

Acknowledgements

The authors are thankful to **Dr. S. N. Thore,** Principal Deogiri College, Aurangabad, and **Dr. B. H. Zaware,** Principal New Arts, Comm. & Science, College, Ahmednagar for constant encouragement and providing necessary facilities. The authors are also thankful to the Director, SAIF, Punjab University, Chandigarh for providing spectral data.

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Received: 14.12.2016.
Accepted: 12.02.2017.