# LPCAS: A New Ionic Liquid for The Eco-Friendly Synthesis of Acridinedione Derivatives Under Solvent Free Condition

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***Abstract*— The synthesis of acridinedione derivatives were achieved via one pot, multicomponent condensation of aromatic aldehydes, dimedone and ammonium acetate utilizing under solvent free condition has been reported. The novel bronsted acidic ionic liquid; L-Pyrrolidine-2-carboxylic acid sulfate (LPCAS) as a catalyst has been used in the Clean, simple, highly efficient and eco-friendly method.**

**This method shows excellent yield of products in shorter reaction time, cleaner reaction profile, environmentally benign nature and the use of inexpensive catalyst.**

***Index Terms*—Acridinedione derivatives, LPCAS, eco-friendly, solvent free, yield etc.**

## I. INTRODUCTION

The methodology for synthesis of acridinedione derivatives is a significant and major task in organic synthesis. Acridinedione derivatives are the vital class of compounds with potential medicinal activity against malaria [1], cancer [2] and leishmania [3]. They are cytotoxic [4] and have ability to bind and damage the DNA [5]. Acridine derivatives have been utilized to produce labeled conjugates with medicinal, peptides, proteins, and nucleic acids [6–8] that exhibit antitumor and DNA-binding properties. In recent years, acridinediones have magnetized eager attention of the researchers due to their use as drugs for cardiovascular diseases, such as angina pectoris [9], hypertension [10-11]. 1, 4-dihydropyridine scaffold present in acridine-1, 8-diones have been shown as potential to reverse multidrug resistance in tumor cell lines [12-13]. The acridinediones also show that evidence of extensive applicability toward photosensitizers and photo polymerization [14].

Acridinedione derivatives have been synthesized by using Hantzsch procedure from condensation of aryl aldehydes, ammonium acetate and dimedone by using the catalysts, such as Methyltrioctylammonium chloride [15], PEG-$SO_3H$ [16], Methane sulfonic acid [17], Silica-supported sulfuric acid [18], Salicylic acid [19], P-TsOH [20], ([CMIM][CF3COO]) [21].

There were some drawbacks from each of these methods. Therefore, an alternative efficient and environmentally benign methodology for synthesis of these acridinedione has been needed. Ionic liquid (ILs) [21-22] showed versatile features such as catalysts, greener reaction media, negligible volatility, thermal stability and remarkable solubility. Out of the abundant ILs developed or available, unfortunately most of ILs showed some amount of solubility in commonly used organic solvents, which creates many problems in product separation.

In this present work, a novel bronsted acidic ionic liquid, L-pyrrolidine-2-carboxylic acid sulfate (LPCAS) [23-27] catalyst has been utilized for the first time in the synthesis of pharmacological potent acridinedione derivatives (Scheme 1) under solvent free condition.

## II. MATERIALS AND METHODS

All the reagents involved in experiment were brought from Aldrich/Merck and used without further purification. The digital melting point apparatus EQ730 (Equiptronics) has been used for the determination of melting points. The completion of reactions and the purity of product were examined on thin layer chromatography using silica gel as a stationary phase and hexane/ethyl acetate as eluent. All the products were characterized by comparing melting points and spectral data with those of authentic samples. The IR spectra were recorded on Schimadzu IR Solution 150SUI spectrophotometer using KBr pellets and values expressed in $cm^{-1}$. The NMR spectra were recorded on Bruker 400 MHz spectrometer using an appropriate solvent and TMS as

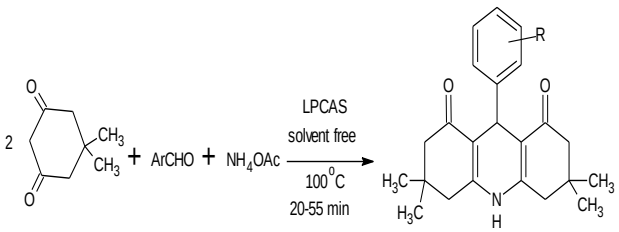
| Sr. No. | Catalysts | Conditions | Time (min.) | Yield (%) | Ref. |
|---|---|---|---|---|---|
| 1 | Methyltrioctylammonium chloride | Ultrasonication /R.T. | 35 | 94 | 15 |
| 2 | PEG-$SO_3H$ | Solvent free /80 $^0$C | 60 | 90 | 16 |
| 3 | Methane sulfonic acid | Solvent free /120 $^0$C | 90 | 92 | 17 |
| 4 | Silica-supported sulfuric acid | $H_2O$/70 $^0$C | 90 | 95 | 18 |
| 5 | Salicylic acid | Solvent free /80 $^0$C | 180 | 82 | 19 |
| 6 | P-TsOH | $H_2O$/Reflux | 480 | 78 | 20 |
| 7 | [CMIM][CF3COO] | aq. EtOH/80 $^0$C | 70 | 90 | 21 |
| 8 | L-Pyrrolidine-2-carboxylic acid sulfate (LPCAS) | Solvent free/100 $^0$C | 55 | 95 | This work |

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

an internal standard. The Mass spectra were predicted on a Jeol JMSD-300 spectrometer.

General procedure for the synthesis of acridinedione derivatives (4a-h):

In 25 ml of round bottom flask, a mixture of aromatic aldehydes 2(a-h) (1 mmol), ammonium acetate **3** (1.5 mmol) and dimedone **1** (2 mmol) and L-pyrrolidine-2-carboxylic acid sulfate (LPCAS) in catalytic amount (1 mmol) was added. This mixture was refluxed at 100 $^0$C under solvent free condition for an appropriate time. The progress and completion of reaction was checked on TLC. After accomplishment of reaction, the reaction mixture was cooled to room temperature and 20 ml of water was added. The separated solid was filtered and recrystallized from ethyl alcohol to offer the pure products (4a-h) as shown in scheme 1.




1 2 (a-j) 3 4(a-h)

Scheme-1: synthesis of acridinedione derivatives

Similarly, the other acridinedione derivatives were prepared using same procedure and reported in Table 1.

Characterization of selected compound:

Compound 4f: $C_{24}H_{29}NO_3$.

FTIR (KBr) (cm $^{1}$):3275, 3180, 3061, 2958, 2831, 1651, 1606, 1365, 1220, 1170, 1035, 837, 815, 534. $^1$H NMR (400 MHz, DMSO): δ ppm 0.86 (s 3H), 0.90 (s 3H), 1.00 (s 3H), 1.02 (s 3H), 2.45 (m 1H), 2.41 (m 1H), 2.32 (m 1H), 2.28 (m 1H), 1.99 (m 1H), 1.95 (m 1H), 2.14 (m 1H), 2.18 (m 1H), 3.67 (s 3H), 4.74 (s 1H), 6.69-6.71 (m 2H), 7.03-7.05 (m 2H), 9.22 (s 1H). m/z: [$M^+$] = 378.14.

## III. RESULTS AND DISCUSSION

The efficiency of L-pyrrolidine-2-carboxylic acid sulfate (LPCAS) IL catalyst has been determined and compared with those of reported acid catalysts in the synthesis of 9-(4-methoxy-phenyl)-3,3,6,6-tetramethyl-3,4,6,7,9,10-hexahydro-2H,5H-acridine-1,8-dione (4a).

In a model reaction, a mixture of benzaldehyde (1 mmol), ammonium acetate (1.5 mmol) and dimedone (2 mmol) and LPCAS (1 mmol) was added to a 25 ml round bottom flask. The mixture was refluxed at 100˚C solvent free condition. The progress and completion of reaction was checked by TLC. After completion of reaction the reaction mixture was cooled to room temperature and 20 ml of water was added. The Separated solid was filtered and purified by recrystallization in ethyl alcohol.

In presence of Methyltrioctylammonium chloride, the reaction proceeds via ultra-sonication method within 35 minutes offering 94 % yield of the product (Sr. No. 1, Table 2). In presence of PEG-$SO_3H$ reaction proceeds at 80 ℃ within 60 minutes offering 90 %

| Sr. No. | Aldehydes | Time (min.) | Yield (%) | Melting Point (°C) | | Ref. |
|---|---|---|---|---|---|---|
| | | | | Observed | Reported | |
| 4a | Benzaldehyde | 55 | 97 | 276-278 | 279-280 | [17] |
| 4b | 2-hydroxy benzaldehyde | 55 | 95 | >300 | >300 | [21] |
| 4c | 4-hydroxy benzaldehyde | 25 | 93 | 286-288 | 284-286 | [21] |
| 4d | 4-Nitro benzaldehyde | 25 | 95 | 260-262 | 261-262 | [21] |
| 4e | 4-chloro benzaldehyde | 40 | 90 | 294-296 | 296-298 | [17] |
| 4f | 4-Methoxy benzaldehyde | 20 | 97 | 268-270 | 270-272 | [17] |
| 4g | 4-Dimethylamino benzaldehyde | 35 | 88 | 260-262 | 263-265 | [17] |
| 4h | 2-chloro benzaldehyde | 20 | 94 | 220-222 | 221-223 | [21] |

Table 1: Synthesis of Acridinedione derivatives catalyzed by IL (4a-h)

yield of the product under solvent free condition (Sr. No. 2, Table 2).

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 55 minutes and offering the product in 95 % (Sr. No. 8, Table 1).

All the above results have showed that, the catalyst proved its efficiency in terms of product yield and reaction times. All of the synthesized compounds (Table 2) are known and structures were confirmed by comparing their melting points with standards.

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 for this synthesis of acridinedione derivatives.

In summary, we have first time reported a new eco-friendly procedure for the synthesis of acridinedione derivatives via one pot condensation of aromatic aryl aldehydes, ammonium acetate and dimedone using L-Pyrrolidine-2-carboxylic acid sulfate as an ionic liquid catalyst under solvent free conditions. The present methodology is consisting of features such as simple procedure, short reaction time, excellent yields and easy separation of catalyst and its reusable behavior. This approach therefore represents a valuable addition to the existing methodology for the synthesis of acridinedione derivatives.

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