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n-Octyl-3-methylpipyridinium bromide ([OMePPy]$^+$Br$^-$): novel ionic liquid to promote green synthesis of polycyclic fused acridines

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ABSTRACT

In this research various polycyclic fused acridines were synthesized via the highly efficient and green one-step four-component reaction between isatins, dimedone, various amines, and dimethylacetylenedicarboxylates (DMAD/DEAD) in the presence of *n*-octyl-3-methylpipyridinium bromide ([OMePPy]$^+$Br$^-$) as a newly prepared ionic liquid, in absolute green situations at room temperature under solvent-free conditions. The ionic liquid characterized by ^{1}H NMR, ^{13}C NMR, GC-MASS, TGA/ DTG, EDX, and FESEM techniques. Utilizing an eco-friendly and simply synthesized ionic liquid, green and economic reaction media, and preparing a wide range of polycyclic fused acridines in good yields are some highlighted aspects of the reported protocol.

***Keywords**: Acridines, Ionic liquid, Isatin, Multi-component reaction (MCR), Green chemistry.*

1. Introduction

Acridine is an *N*-containing heterocycle that is also a widespread building block in many organics. Several interesting compounds possess acridine motif. They could also be joined to other heterocycles to obtain poly fused structures that consist of multiple properties such as antidiabetic [1], anticancer [2], thermally activated delayed fluorescence (TADF) [3], DNA-intercalating antitumor [4], DNA-binding antitumor [5], anti-prion [6], and antibacterial/antifungal [7] activities. Recently various polycyclic functionalized organics containing acridine scaffold have been synthesized through different protocols such as three-component reaction of aromatic aldehydes, 1,3-dicarbonyl compounds, and 1*H*-indol-5-amine in the absence of solvent [8], cyclization reaction of isatins, dimedone, and 5-aminoindazole [9], water-mediated pseudo-four component condensation of dimedone, anilines, and isatin by *β*-cyclodextrin [10], three-component condensation of isatins, thioamides/ thioureas, and dimedone [11], solvent-free three-component reaction of dimedone, anilines, and isatins by acetic acid [12], iodocyclization reactions [13], regioselective microwave-assisted three-component reaction of aromatic aldehydes, 2-hydroxy-1,4-naphthoquinone, indazol-5-amine in HOAc [14], four-component domino multicyclization in isobutyric acid under microwave irradiation [15], Brønsted acid-accelerated domino reactions between indoline-2,3-dione and C_2-tethered indol-3-yl enaminones [16], and three-component reaction of anilines, aldehydes and cyclic 1,3-dicarbonyls promoted by three class of catalyst which are i) *N*,*N*′-dibromo-*N*,*N*′-1,2-ethanediylbis(*p*-toluenesulfonamide) [BNBTS] under solvent-free conditions [17], ii) graphene oxide incorporated strontium magnetic nanocatalyst (MSrGO NCs) under solvent-free conditions [18], and iii) camphor sulfonic acid (CSA) in heated ethanol [19]. In 2015 Sarkar and Mukhopadhyay prepared five ring fused acridines through the four-component reaction of dimedone, amines, isatins, and dialkylacetylenedicarboxylate in a 100 °C PEG/ H_2O (1:3) media in the presence of 25-hydroxy-26,27,28-tris(1-carboxy-1-methylmethoxy)-*p*-*tert*-butylcalix[4]arene (C4a) within 12 h [20].

Recently ionic liquids (ILs) attended special attentions as environmentally-friend-alternatives for the volatile organic solvents [21]. Various kinds of ILs gained great interest to promote different classes of organic transformations [22-24]. They could also play a dual role of catalyst and/ or media in organic reactions which

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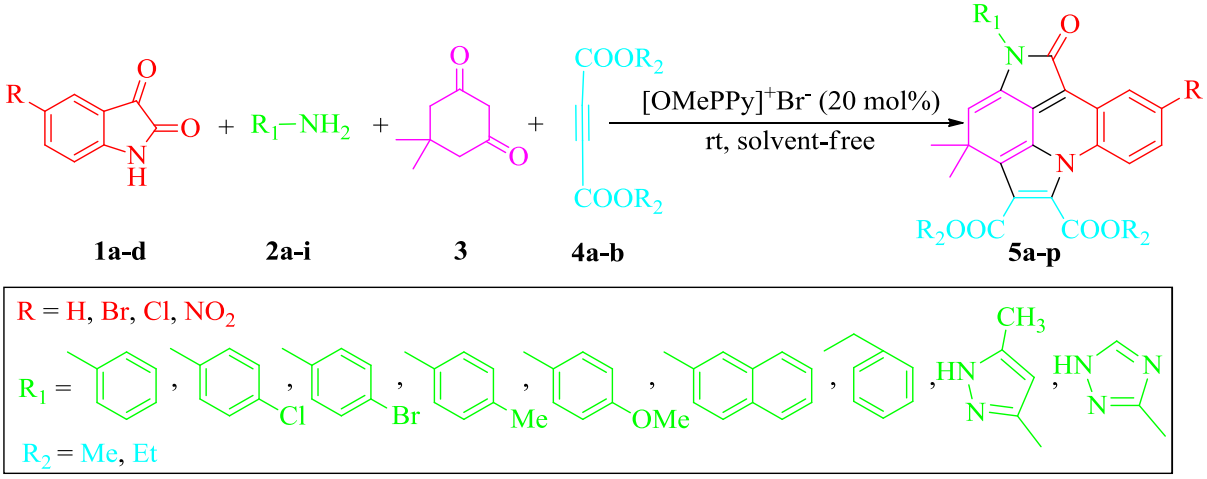
enhance their efficacy in green as well as economic chemistry [25-27].

In following of our research interest to prepare novel nanocatalysts and also functionalized poly heterocyclic compounds under green media [28-32], herein we reported *n*-octyl-3-methylpipyridinium bromide ([OMePPy]$^+$Br$^-$) as a novel ionic liquid to promote synthesis of some poly fused acridines via the four-component condensation of dimedone, isatins, aliphatic/ aromatic amines, and DMAD/ DEAD under absolute green media in the absence of solvent at room temperature (**Scheme 1**).



Scheme 1. Synthesis of polycyclic fused acridines in the presence of [OMePPy]$^+$Br$^-$ IL.

2. Experimental

2.1. Materials and equipments

Chemicals and solvents were purchased from the Merck and Sigma-Aldrich companies and used without further purification. Melting points were determined in capillary tubes on Electrothermal 9200 melting point apparatus and are uncorrected. FT-IR spectrum recorded on Bruker FT-IR, Tensor 27 spectrometer on KBr discs. The size and morphology of the nanostructures was visualized by SEM FEI Quanta 200 Scanning Electron Microscope. Centrifuge machine (UNIVERSAL 320, 1000 W) was used for the preparation process of nanocatalyst. The ^{1}H NMR and ^{13}C NMR spectra were obtained by Bruker drx (300 MHz and 75 MHz) spectrometer in DMSO-d_6 as solvent. The mass spectra were recorded on a GC-Mass (5973 Network Mass Selective Detector, GC 6690 Agilent) and also (Mass l 5973 Network Mass Selective Detector, Agilent Technology (HP) Agilent) instruments. Thermal gravimetric analysis (TGA) was recorded by TGA1 METTLER TOLEDO.

2.2. Synthesis of n-octyl-3-methyl-pipyridinium bromide ([OMePPy]$^+$Br$^-$)

To a solution of 1-bromooctane (10 mmol, 0.96 g) in EtOAc (20 mL), a mixture of 2-methylpipyridine (10 mmol, 0.931 g) in EtOAc (10 mL) was added through a dropping funnel drop by drop at room temperature. The mixture was then refluxed at 100 ˚C for 8 h. The result was centrifuged (10000 rpm) and the solid residue washed with further EtOAc (3 × 10 mL) and air dried over night to obtain ([OMePPy]$^+$Br$^-$) as a brown solid (m.p. = 150 ˚C). FT-IR (KBr): 3421, 2948, 1636, 1461, 1384, 933 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): 1.19 (brs, 3H, CH_3), 1.22 (brs, 3H, CH_3), 1.32-1.48 (m, 7H, CH_2), 1.42-1.63 (m, 4H, CH_2), 1.68-1.77 (m, 7H, CH_2), 2.77-2.85 (m, 2H, CH_2), 3.07-3.09 (m, 1H, CH), 3.17-3.21 (m, 2H, CH_2), 8.54 5.64 (brs, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 18.76, 21.47, 21.60, 29.88, 40.33, 43.39, 51.73. MS (EI) (*m/z*): 292 [M$^+$], 277 [M$^+$]-Me, 263 [M$^+$]-Me, -CH_2, 248 [M$^+$]-2Me, -CH_2, 220 [M$^+$]-2Me, -$(CH_2)_3$, 182 [M$^+$]-2Me, -Br, 168 [M$^+$]-2Me, -CH_2, -Br, 111 $[BrCH_2NH_3]^+$, 99 $[(CH_2)_6CH_3]^+$, 84 $[(CH_2)_5CH_3]^+$, 43 [isopropyl]$^+$.

2.3. General procedure for the synthesis of five ring fused acridines

A mixture of dimedone **1** (1 mmol), amines **2a-i** (1 mmol), isatins **3a-d** (1 mmol), and dialkyl acetylene dicarboxylate **4a-b** (1.3 mmol) in the presence of [OMePPy]$^+$Br$^-$ (20 mol%) was stirred magnetically under solvent-free conditions at room temperature up to completion monitored by TLC (petroleum ether/EtOAc, 2:1). The residue was then submitted to plate chromatography (PLC) to get the pure products **5a-p**.

2.4. Characterization data of the new compounds

Dimethyl-4,4-dimethyl-2-(5-methyl-1*H*-pyrazol-3-yl)-10-nitro-1-oxo-2,4-dihydro-1*H*-dipyrrolo[3,2,1-*de*:4',3',2'-*mn*]acridine-5,6-dicarboxylate **(5o):** Dark yellow solid; m.p. = 95-97 ˚ C. FT-IR (KBr): 3423, 2958, 2930, 1738, 1612, 1523, 1384 cm^{-1}. ^{1}H NMR (300

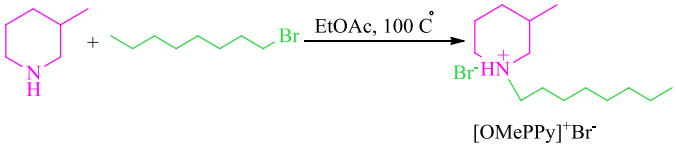
MHz, DMSO-d_6): 0.94 (s, 6H, $2CH_3$), 2.01 (brs, 3H, CH_3), 3.72-3.78 (brs, 6H, 2OMe), 6.42 (s, 1H, Ar), 7.81 (s, 1H, Ar), 6.89-7.19 (m, 2H, Ar), 8.08-8.44 (m, 1H, Ar), 10.75 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 178.08, 149.30, 141.68, 135.44, 125.88, 118.19, 109.11, 77.56, 47.72, 41.02, 12.32, 31.77, 27.82, 27.51

Dimethyl-4,4-dimethyl-10-nitro-1-oxo-2-(1*H*-1,2,4-triazol-3-yl)-2,4-dihydro-1*H*-dipyrrolo[3,2,1-*de*:4',3',2'-*mn*] acridine-5,6-dicarboxylate **(5p):** Dark yellow solid; m.p. = 152-154 ° C. FT-IR (KBr): 3425, 2957, 2929, 1718, 1668, 1624, 1522, 1453, 1385 cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6): 0.94 (brs, 6H, $2CH_3$), 2.01 (s, 3H, OMe), 2.08 (s, 3H, OMe), 6.87 (s, 1H, Ar), 7.79 (brs, 1H, Ar), 8.01-8.09 (m, 2H, Ar), 8.15-8.20 (m, 1H, Ar), 10.65 (s, 1H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): 178.22, 176.56, 159.46, 149.26, 141.58, 135.79, 129.01, 125.70, 118.08, 108.45, 107.40, 77.61, 48.01, 31.73, 27.87.

3. Results and Discussion

3.1 Characterization of [OMePPy]$^+$Br$^-$ IL

The simple procedure for the synthesis of [OMePPy]$^+$Br$^-$ IL is illustrated in **Scheme 2**. It has been characterized by ^{1}H NMR, ^{13}C NMR, GC-MASS, TGA/ DTG, EDX, and SEM techniques.



Scheme 2. *n*-Octyl-3-methylpipyridinium bromide ([OMePPy]$^+$Br$^-$) IL.

Fig. 1 demonstrates the EDAX result of [OMePPy]$^+$Br$^-$ IL. The analysis affirmed presentation of C (23.4%), N (10.9%), O (12.79%), and Br (52.91%) in the obtained nanostructure that proved its successful preparation.

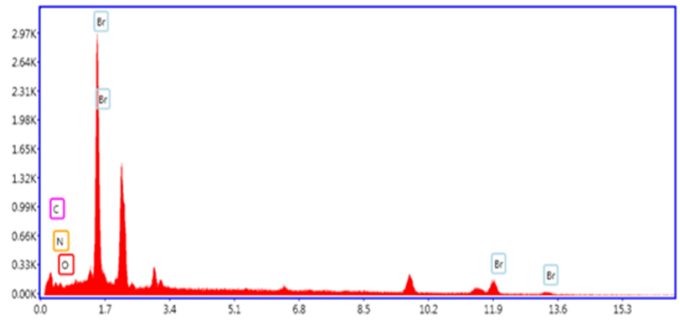


Fig. 1. The EDAX pattern of [OMePPy]$^+$Br$^-$ IL.

The morphology of [OMePPy]$^+$Br$^-$ IL is illustrated in **Fig. 2**. As can be seen, some rod-shaped in 2-10 µm has been obtained but no uniform nano-scale observed. Few nanoparticles with an average diameter of 25-100 nm were obtained in the whole mass of the IL.

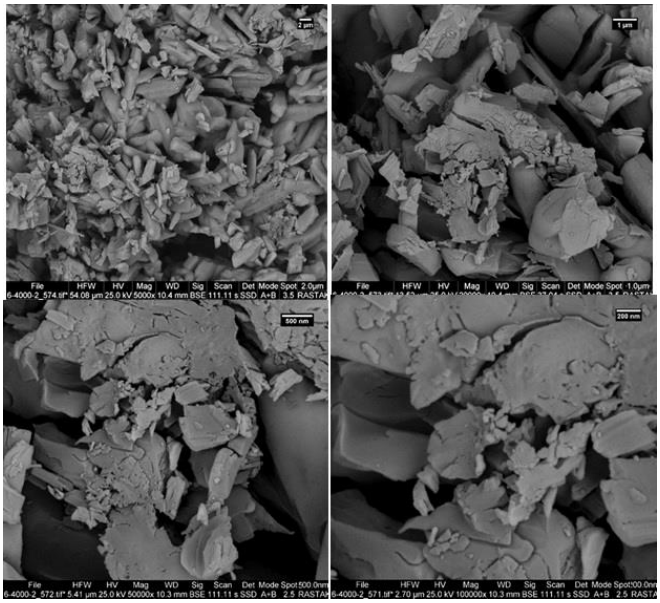


Fig. 2. FESEM images of [OMePPy]$^+$Br$^-$ IL.

TGA/ DTG analysis of the ionic liquid [OMePPy]$^+$Br$^-$ is investigated in **Fig. 3**. Thermal degradation of the IL started at 220 °C with a weight loss of about 10 %. Total decay occurs at 340 °C. Therefore, the [OMePPy]$^+$Br$^-$ is thermally stable up to 220 °C, which is an interesting characteristic due to its total organic framework.

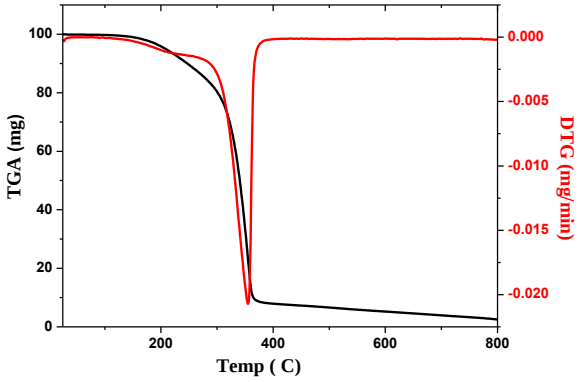


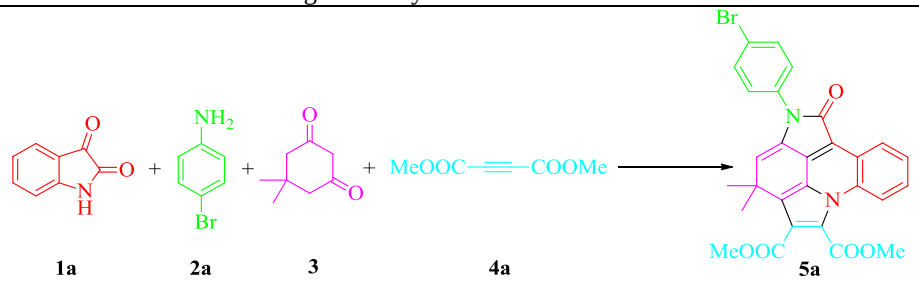
Fig. 3. TGA/ DTG curve of [OMePPy]$^+$Br$^-$.

3.2 Investigation of the catalytic activity

Initially, to optimize the reaction conditions, the four-component reaction of isatin **1a** (1 mmol), 4-bromoaniline **2b** (1 mmol), dimedone **3** (1 mmol), and dimethylacetylenedicarboxylate (DMAD) **4a** (1.3 mmol) was chosen as a model reaction to obtain the corresponding dimethyl 2-(4-bromophenyl)-4,4-dimethyl-1-oxo-2,4-dihydro-1H-dipyrrolo[3,2,1-de:4',3',2'-mn]acridine-5,6-dicarboxylate **5a**, as a poly fused-ring heterocyclic system. Based on the data in

Table 1, the optimum amount of IL was 20 mol% (0.06 g) (entries 1-3). Elevating the amount up to 40% (0.12 g) decreased the yield due to surface absorbent of the catalyst on the substrates that prevent its catalytic role. The model examined in different solvents (entries 4 & 5) but the best choice was solvent-free conditions. The model performed under solvent-less 70 °C media but the result was not satisfactory (entry 6). Finally ultrasound irradiation was used as a powerful tool which was not effective for preparing 5a (entry 7). In the final step, to optimize conditions, the model was performed in the absence of IL. The result (entry 8) demonstrated the low percentage progress in long time, which affirmed the effective catalytic activity of $[OMePPy]^+Br^-$.

Table 1. The reaction conditions screening for the synthesis of **5a**



1a **2a** **3** **4a** **5a**

Entry	Conditions Solvent (5 mL)/ Temp. (°C)/ $[OMePPy]^+Br^-$ (mole%)	Time (min)	Yield (%)[a]
1	-/ rt/ 10	150	35
2	-/ rt/ 20	90	90
3	-/ rt/ 40	120	50
4	EtOH/ rt/ 20	120	70
5	H_2O/ rt/ 20	120	60
6	-/ 70/ 20	120	70
7	EtOH/ rt/ 20 (US irradiation/ 60 Wcm^{-1})	40	45
8	-/ rt/ -	200	15

[a]Isolated yields.

In the next step, to generalize the approach, derivatization of acridines is done by using a vast range of substrates in the presence of 20 mol% (0.06 g) $[OMePPy]^+Br^-$ at room temperature under solvent-free conditions. The results summarized at **Table 2**. It demonstrated different anilines reacted with isatin, DMAD, and dimedone to gain the corresponding dimethyl 2-(aryl)-4,4-dimethyl-1-oxo-2,4-dihydro-1*H*-dipyrrolo[3,2,1-*de*:4',3',2'-*mn*]acridine-5,6-dicarboxylates **5a-c** successfully. Benzyl amine was another effective candidate to perform this reaction to obtain **5d**. Then, DEAD utilized in this four-component condensation resulted in interesting acridines **5e-h**. Then 5-chloro- and 5-bromo isatin was examined for this condensation with different amines and DMAD/DEAD to get the desired products **5i-n**. In the final section, two pharmaceutically potent hetero-aromatic amines, 5-methyl-3-aminopyrazol and 3-amino-1,2,4-triazole, were reacted with DMAD, 5-nitroisatin and dimedone to afford **5o-p**.

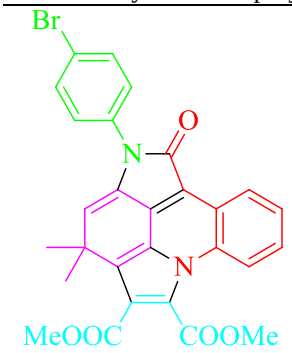
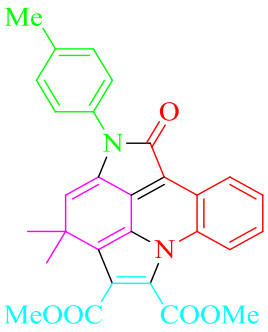
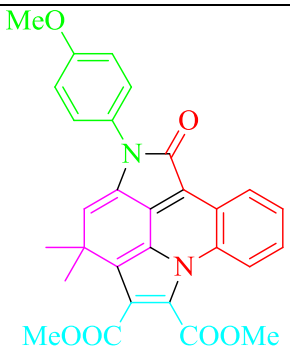
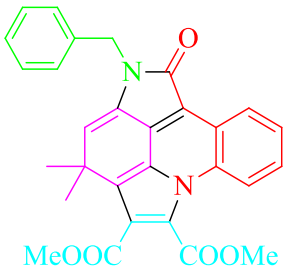
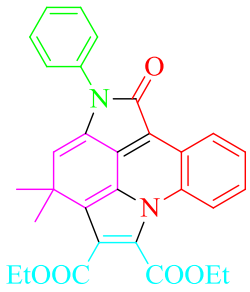
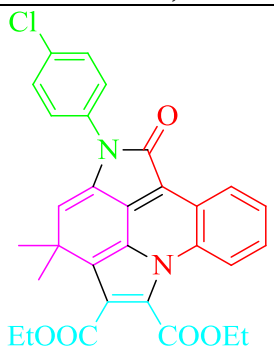
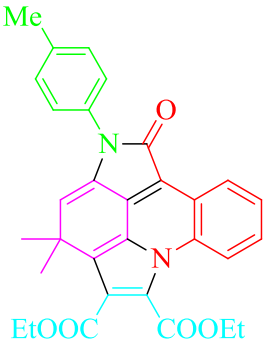
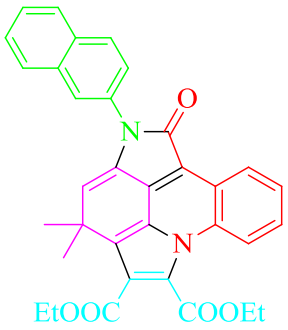
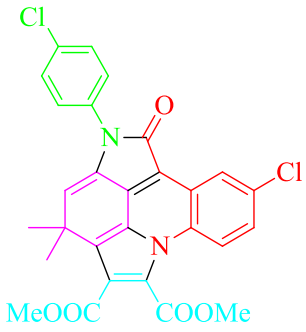
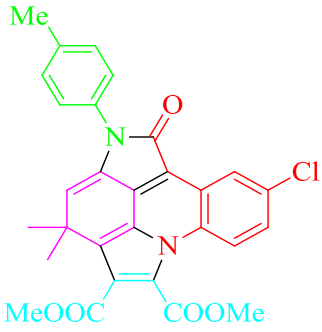
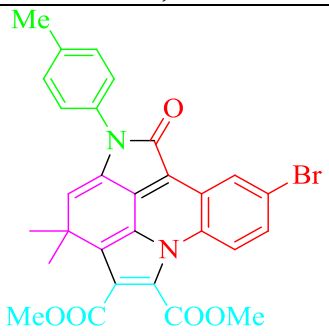
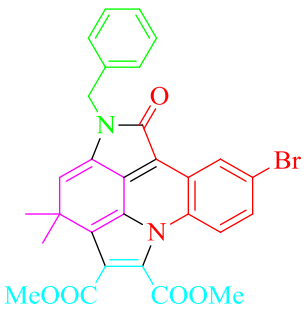
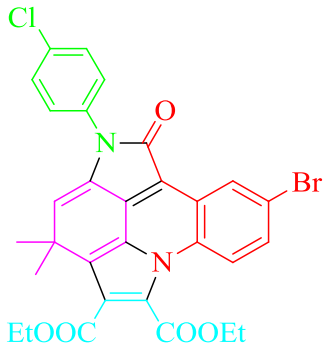
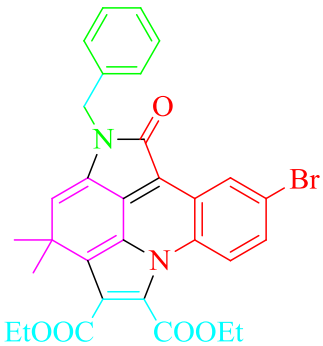
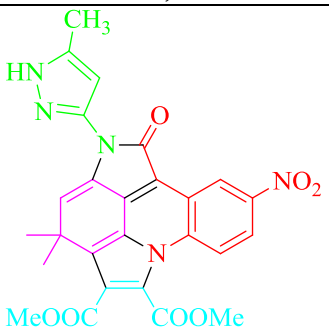
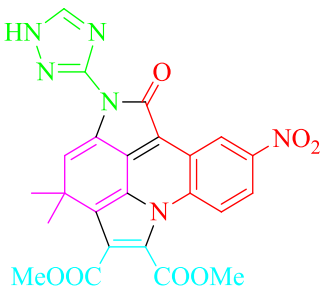
A proposed mechanism is illustrated in **Scheme 3**. The nucleophilic attack of amine **2** to activated dimedone **A** gained enaminoketone **B** which underwent the reaction with isatin **3** to obtain intermediate **C**. Dehydration of **C** followed by intramolecular ring closure yielded **E** that condensed to **F**. Final ring closure of **F** with acetylenedicarboxylate **4** achieved the desired product **5**.

Finally to affirm of the protocol efficiency, a comparative study for the synthesis of dimethyl 2-benzyl-10-bromo-4,4-dimethyl-1-oxo-2,4-dihydro-1*H*-dipyrrolo[3,2,1-*de*:4',3',2'-*mn*]acridine-5,6-dicarboxylate **5l** is represented in **Table 3**.

4. Conclusions

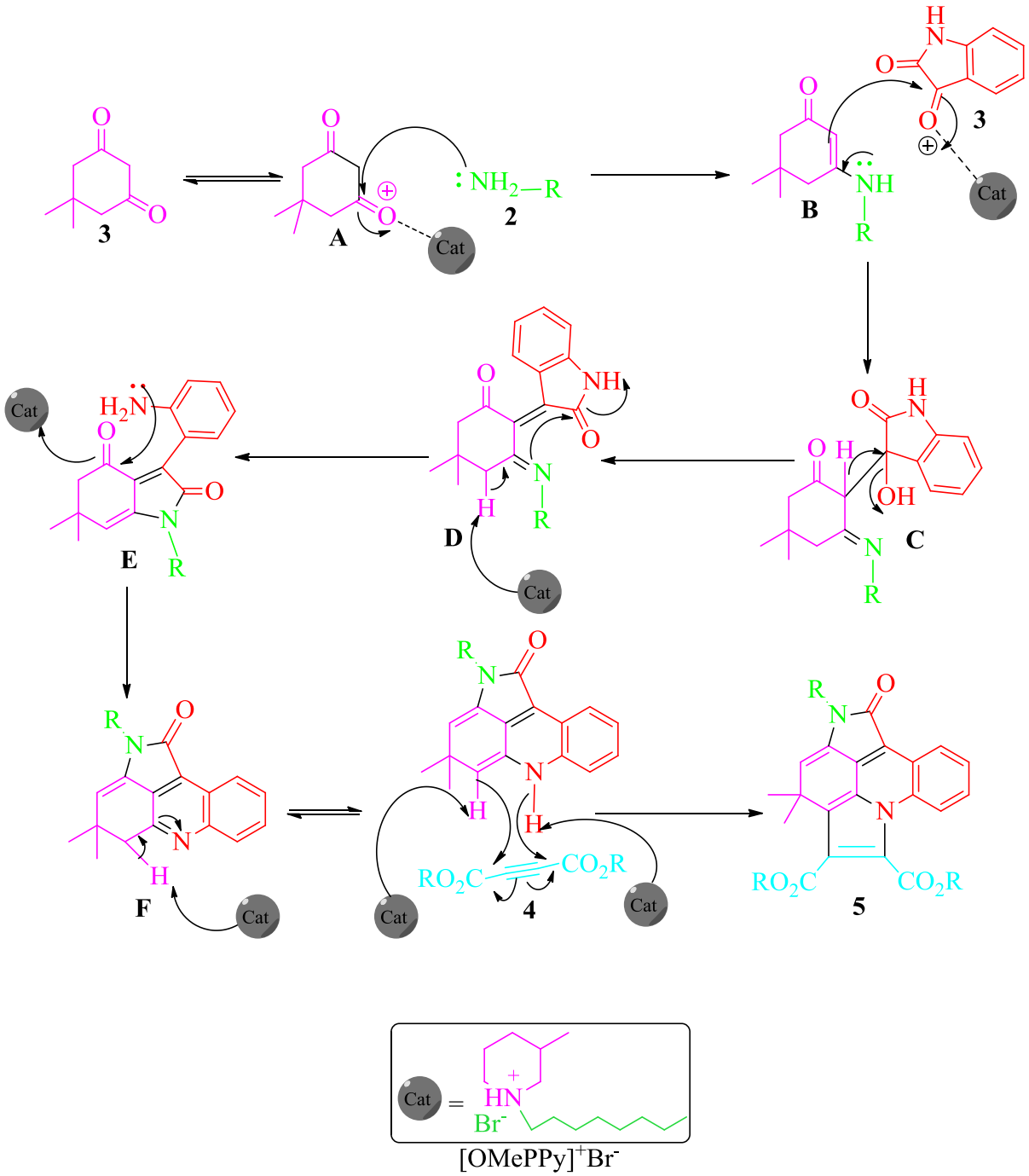
In conclusion, polycyclic fused acridines have been obtained under a complete green economic situation in the presence of $[OMePPy]^+Br^-$, as a novel IL, through the one-step four-component reaction of isatins, dimedone, amines, and dimethylacetylenedicarboxylate (DMAD/ DEAD) successfully. The protocol has some highlighted features which are: a) utilizing an eco-friendly and simply prepared IL, as promoter, b) lacking any hazardous solvents and also heat source to perform the mentioned MCR in the reaction media, c) preparing a vast range of polycyclic fused acridines under absolute green conditions with good yields.

Table 2. Synthesis of polycyclic fused acridines.

 **5a** 90 min, 90%[a]	 **5b** 45 min, 88%	 **5c** 75 min, 86%	 **5d** 30 min, 84%
 **5e** 30 min, 91%	 **5f** 90 min, 95%	 **5g** 60 min, 84 %	 **5h** 45 min, 90%
 **5i** 30 min, 93%	 **5j** 60 min, 88%	 **5k** 45 min, 87%	 **5l** 75 min, 91%
 **5m** 45 min, 91%	 **5n** 45 min, 87%	 **5o**[b] 45 min, 89% 95-97 °C (new)	 **5p**[b] 45 min, 88% 152-154 °C (new)

[a] Isolated yields.

[b] The compounds 5o-p are new. The reference for 5a-n is 20.



Scheme 3. Proposed mechanism for the synthesis of five ring fused acridines.

Table 3. Comparison of the efficiency of $[OMePPy]^+Br^-$ with the previously reported catalysts in the synthesis of **5l**.

Entry	Conditions Catalyst (g, mol%)/ Temperature (°C)/ Solvent (ml)	Time (h)	Yield (%)	[Ref]
1	C4a (0.043, 5 mol%)/ 100 °C/ PEG/H_2O: 1/3 (5)	12	70	[20]
2	$[OMePPy]^+Br^-$ (0.06, 20 mol%)/ rt/ -	1.25	91	This work

C4a: 25-Hydroxy-26, 27, 28-tris(1-carboxy-1- methylmethoxy)-*p*-tert-butylcalix[4]arene

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