HEPES BUFFER MEDIATED SYNTHESIS OF 3,4-DIHYDRO-3,3-DIMETHYL-9-ARYLACRIDIN-1-ONES

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One-pot three-component synthesis of 3,4-dihydro-3,3-dimethyl-9-phenylacridin-1(2H,9H,10H)-one derivatives has been described by the cyclocondensation of aromatic aldehydes, aromatic amines and dimeredone in the presence of 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) in ethanol at reflux condition. Besides buffering agent, HEPES as an organocatalyst has been used for the first time in multicomponent organic transformation and succeeded along with various merits of green chemistry practices. The reaction is mechanized by zwitterionic interactions between organocatalyst and reactants to form targeted molecules.

INTRODUCTION

Nowadays, the time has come to expand the horizon of our conscious foresight about environmental consequences and its inequality in the world that leads to natural disasters. It is expected from all the chemists and co-workers while performing any chemical transformations in the laboratory. Therefore, chemists have to modify the protocols or keep control of it so that the developed methodology can help to protect human health and maintains the environment unaffected. Keeping these factors in view, it was thought worthiness to synthesize 3,4-dihydro-3,3-dimethyl-9-phenylacridin-1-ones by means of buffer mediated organocatalyst with conventional techniques. In literature buffering activity of HEPES is widely utilized to maintain local pH of the biochemical, biological reactions and environmental studies, 1-3 for the synthesis of specific sized nanogold particles, 4 detection of ATP in clinical applications, 5 to study function characteristics of hemoglobin. 6

Beside this other various organocatalysts have been extensively used for the synthesis of different heterocyclic organic compounds through C-C and C-heteroatom bond formation reactions. 7,8 The catalytic proficiency of an organocatalyst is quite significant and beneficient than biocatalysts and metal catalysts toward organic transformations. The mechanistic role of an organocatalyst for the initiation or the activation of the reactant molecule is either by providing or removing protons or electrons for the reacting species. 9

Our targeted molecule based on the acridine nucleus is very versatile in pharmacological behavior such as a wide range of anesthetic activity viz surface anesthesia, infiltration anesthesia, peripheral and spinal anesthesia, etc., antimarial agent, antiseptic and anticancer agents. 10,11 Other few literature reports revealed that acridine moiety shows antibacterial activity, antifungal activity, 12 antiproliferative activity 13 and antioxidant. 14 Because of the wide spectrum of medicinal activity chemists have attempted to synthesize acridine derivatives by several ways that have been discussed in the reported review and multi-step synthetic routes under different reaction conditions and use of various reagents by conventional and non-conventional as well. 15 Some multicomponent methodologies have also been reported, like protic pyridinium ionic liquid, 16 L-proline, 17 nano ferrite 18, etc. However, aspects of green chemistry need some more effort that could develop sustainable protocols.

Therefore, we used HEPES buffering agent preferentially as an organocatalyst, which found to be smart and compatible in various reaction conditions with a variety of substrates and contributes a part of green chemistry.

EXPERIMENTAL

All the reagents and solvents were used for the reactions and column chromatography was purchased from HiMedia, Finechem, Spectrochem and Rankem chemical companies and used directly without further purification. The progress of the reactions was monitored by Thin Layer chromatography 60 F254 (TLC). 1H NMR spectra were recorded on 300 MHz FT-NMR spectrometer in CDCl3 as a solvent and chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane (CH3)4Si.

Experimental procedure for the preparation of 3,4-dihydro-3,3-dimethyl-9-phenylacridin-1(2H,9H,10H)-one derivatives

In the hard glass test tube benzaldehyde (0.221 g, 0.002 mol) and aniline (0.193 g, 0.002 mol ) and HEPES (40 mg) in 25 mL ethyl alcohol were stirred at reflux temperature for 30-35 minutes. To this solution, dimeredone (0.290g, 0.002 mol) was added portion wise with continued stirring at same temperature. The progress of the reaction was monitored after interval of each half hour by TLC. The reaction is completed after specified period of time. After completion the reaction mixture was poured on crushed ice. The obtained solid was filtered, dried and purified by recrystallization in ethanol to yield a pure product. Similar procedure was applied for the synthesis of other derivatives. All compounds were characterized by spectroscopic analysis.
3,4-Dihydro-3,3-dimethyl-9-phenylacridin-1(2H,9H,10H)-one (4a)

M. P. 170-172 °C; ¹H NMR (CDCl₃) δ ppm; of 10.12 (S, 1H, N-H), 6.45 - 7.85 (m, 9H, Ar-H), 5.55 (S, 1H, C-H). 3.01 (q, 4H, CH₂, J= 24.6), 1.75 (S,6H, CH₃); MS m/z = 303.14; IR (KBr); ν cm⁻¹ 3055 (N-H Str.), 3006 (C-H Str.),1674 (C=O Str.), 1500 (C=C Str.).

9-(4-Chlorophenyl)-3,4-dihydro-3,3-dimethylacridin-1(2H,9H,10H)-one (4b)

M. P. 167-169 °C; ¹H NMR (CDCl₃) δ ppm; of 9.98 (S, 1H, N-H), 7.12 (d, 2H, Ar-H, J= 1.3), 7.34 (S, 1H, Ar-H), 6.90 - 7.15 (m, 5H, Ar-H), 4.96 (S, 1H, C-H), 3.07 (S, 4H, CH₂), 2.15 (S,6H, CH₃); MS m/z = 337.17; IR (KBr); ν cm⁻¹ 3109 (N-H Str.), 3004 (CH₃ Str.),1778 (C=O Str.), 1429 (C=C Str.).

7-Chloro-3,4-dihydro-3,3-dimethyl-9-phenylacridin-1(2H,9H,10H)-one (4c)

M. P. 188-190 °C; ¹H NMR (CDCl₃) δ ppm; of 10.02 (S, 1H, N-H), 7.82 (d, 2H, Ar-H, J= 1.9), 7.34 (S, 1H, Ar-H), 6.90 - 7.15 (m, 5H, Ar-H), 4.96 (S, 1H, C-H), 3.07 (S, 4H, CH₂), 2.15 (S,6H, CH₃); MS m/z = 337.30; IR (KBr); ν cm⁻¹ 3055 (N-H Str.), 3004 (CH₃ Str.),1778 (C=O Str.), 1429 (C=C Str.), 760 (C-Cl Str.).

3,4-Dihydro-3,3-dimethyl-9-p-tolylacridin-1(2H,9H,10H)-one (4d)

M. P. 199-201 °C; ¹H NMR (CDCl₃) δ ppm; of 9.42 (S, 1H, N-H), 7.15 - 7.78 (m, 8H, Ar-H), 4.74 (S, 1H, C-H), 2.81 (q, 4H, CH₂, J= 24.7), 1.75 (S,6H, CH₃), 2.25 (S,3H, CH₃); MS m/z = 329.17; IR (KBr); ν cm⁻¹ 3130 (N-H Str.), 2796 (CH₃ Str.),1648 (C=O Str.), 1290 (C=C Str.).

3,4-Dihydro-9-(4-hydroxy-3-methoxyphenyl)-3,3-dimethylacridin-1(2H,9H,10H)-one (4e)

M. P. 145-147 °C; ¹H NMR (CDCl₃) δ ppm; of 9.98 (S, 1H, N-H), 7.12 (d, 2H, Ar-H, J= 1.4), 7.30 (d, 2H, Ar-H, J= 8.10), 6.45 - 6.99 (m, 4H, Ar-H), 4.75 (S, 1H, C-H), 2.67 (S, 4H, CH₂), 1.15 (S,6H, CH₃), 5.98 (S, 1H, O-H); MS m/z = 349.12; IR (KBr); ν cm⁻¹ 3110 (N-H Str.), 2796 (CH₃ Str.),1648 (C=O Str.), 1290 (C=C Str.).

3,4-Dihydro-3,3,7-trimethyl-9-phenylacridin-1(2H,9H,10H)-one (4f)

M. P. 158-160 °C; ¹H NMR (CDCl₃) δ ppm; of 9.42 (S, 1H, N-H), 7.15 - 7.78 (m, 8H, Ar-H), 4.74 (S, 1H, C-H), 2.81 (q, 4H, CH₂, J= 24.7), 1.75 (S,6H, CH₃), 2.05 (S,3H, CH₃); MS m/z = 317.28; IR (KBr); ν cm⁻¹ 3130 (N-H Str.), 2796 (CH₃ Str.),1648 (C=O Str.), 1290 (C=C Str.).

3,4-Dihydro-3,3,7,3-trimethyl-9-(4-nitrophenyl)acridin-1(2H,9H,10H)-one (4g)

M. P. 197-199 °C; ¹H NMR (CDCl₃) δ ppm; of 10.95 (S, 1H, N-H), 8.02 (d, 2H, Ar-H, J= 1.3), 7.94 (S, 1H, Ar-H), 7.30 (d, 2H, Ar-H, J= 9.75), 7.09 (S, 1H, Ar-H), 5.60 (S, 1H, C-H), 2.51 (q, 4H, CH₂, J= 24.6), 2.02 (S, 3H, CH₃), 1.20 (S,6H, CH₃); MS m/z = 364.4; IR (KBr); ν cm⁻¹ 3065 (N-H Str.), 2937 (CH₃ Str.), 1721 (C=O Str.), 1520 (-NO₂ Str.), 1461 (C=C Str.).

3,4-Dihydro-3,3,9-trimethylacridin-1(2H,9H,10H)-one (4i)

M. P. 120-122 °C; ¹H NMR (CDCl₃) δ ppm; of 4.22 (S, 1H, N-H), 6.45 - 6.85 (m, 4H, Ar-H), 4.77 (S, 1H, C-H), 2.15 (q, 4H, CH₂, J= 24.6), 1.25 (S,6H, CH₃), 1.45 (S,3H, CH₃); MS m/z = 241.10; IR (KBr); ν cm⁻¹ 3110 (N-H Str.), 2967 (CH₂ Str.),1615 (C≡C Str.), 1400 (C=C Str.).

RESULTS AND DISCUSSION

To take a broad view of an experimental procedure, we have optimized the reaction conditions by several methods, out of which few successful reports have been demonstrated here with this discussion. Previously, we fruitfully attempted to establish such conventional and non-conventional methods for the preparation of various heterocyclic compounds.¹⁹,²⁰

For the synthesis of 3,4-dihydro-3,3-dimethyl-9-phenylacridin-1(2H,9H,10H)-one (4) initially, in the hard test tube we refluxed benzaldehyde (1), aniline (2) and dimedone (3) with constant stirring in the presence of HEPES as a organocatalyst in ethanol as a reaction medium (Scheme 1).

![Scheme 1](http://dx.doi.org/10.17628/ecb.2020.9.6-9)
After several experimental attempts, we came to know that reaction proceeds to completion by proper sequential addition of reactant and catalyst. Accordingly, benzaldehyde, aniline and HEPES were refluxed for 30-35 minutes yellow coloration is observed in the reaction vessel, which indicates the formation of Schiff’s base as an intermediate.

Table 1. Screening of solvents for model reaction (preparation of 1).

<table>
<thead>
<tr>
<th>No.</th>
<th>Solvent</th>
<th>Time, h</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Methanol</td>
<td>5.50</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>Ethanol</td>
<td>3.00</td>
<td>95</td>
</tr>
<tr>
<td>3</td>
<td>Isopropyl alcohol</td>
<td>5.50</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>Aqueous alcohol (1:1)</td>
<td>11.50</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>Acetone</td>
<td>5.50</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>DCM</td>
<td>7.20</td>
<td>60</td>
</tr>
<tr>
<td>7</td>
<td>Chloroform</td>
<td>6.00</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>Ethyl acetate</td>
<td>6.20</td>
<td>50</td>
</tr>
</tbody>
</table>

Later on, dimedone is added in that reaction vessel portion-wise under the same reaction condition that leads to the formation of the targeted product by cyclocondensation manner within the next couple of hours. To establish the optimized protocol, we examined different proic-non proic and polar-nonpolar solvents such as alcohols, aqueous alcohol, acetone, dichloromethane (DCM), chloroform, ethyl acetate, etc. (Table 1) and a stoichiometric study has also been completed (Table 2).

Table 2. Effect of catalyst concentration on model reaction.

<table>
<thead>
<tr>
<th>Sr.</th>
<th>Catalyst, mg</th>
<th>Time, h</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>3</td>
<td>40</td>
</tr>
<tr>
<td>3</td>
<td>30</td>
<td>3</td>
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</tr>
<tr>
<td>4</td>
<td>40</td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>50</td>
<td>3</td>
<td>80</td>
</tr>
</tbody>
</table>

After the successful screening of suitable solvent and stoichiometry determination for catalyst, it has been reported that synthesis of 3,4-dihydro-3,3-dimethyl-9-phenylacridin-1(2H,9H,10H)-one by the cyclocondensation of benzaldehyde, aniline and dimedone in the presence of HEPES as an organocatalyst in ethanol as a reaction medium.

To take a broad view, the set procedure has been implemented for various aldehydes and anilines to produce different derivatives of 3,4-dihydro-3,3-dimethyl-9-phenylacridin-1(2H,9H,10H)-one (Table 3).

Table 3. HEPES catalyzed synthesis of 3,4-dihydro-3,3-dimethyl-9-phenylacridin-1(2H,9H,10H)-one derivatives.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R/Aldehyde</th>
<th>R’/Amine</th>
<th>Time, h</th>
<th>Yield, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>H</td>
<td>H</td>
<td>3</td>
<td>79</td>
</tr>
<tr>
<td>4b</td>
<td>4-Cl</td>
<td>H</td>
<td>3</td>
<td>79</td>
</tr>
<tr>
<td>4c</td>
<td>H</td>
<td>4-Cl</td>
<td>3</td>
<td>71</td>
</tr>
<tr>
<td>4d</td>
<td>4-CH₃</td>
<td>H</td>
<td>3</td>
<td>78</td>
</tr>
<tr>
<td>4e</td>
<td>4-OH, 3-OCH₃</td>
<td>H</td>
<td>3</td>
<td>70</td>
</tr>
<tr>
<td>4f</td>
<td>H</td>
<td>3-CH₃</td>
<td>3</td>
<td>72</td>
</tr>
<tr>
<td>4g</td>
<td>3-NO₂</td>
<td>4-CH₃</td>
<td>3</td>
<td>69</td>
</tr>
<tr>
<td>4h</td>
<td>4-NC(=O)</td>
<td>H</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>4i</td>
<td>Acetaldehyde</td>
<td>H</td>
<td>3</td>
<td>64</td>
</tr>
<tr>
<td>4j</td>
<td>Furfuraldehyde</td>
<td>H</td>
<td>3</td>
<td>69</td>
</tr>
</tbody>
</table>

During derivatization, it has been noted that aromatic aldehydes and anilines with different substitutions at different positions have been reacted smoothly with appreciable product yield. In conjunction with an output of the reaction in our hand, heterocyclic reactants also give a compatible yield of the product, whereas aliphatic aldehyde resulted in comparatively less yield and took more time for transformation. The formation of products was confirmed by their physical constant and structures were elucidated by spectroscopic analysis.

CONCLUSIONS

We have developed a sustainable protocol, which will be the user-friendly synthetic route for pharmacodynamic 3,4-dihydro-3,3-dimethyl-9-phenylacridin-1(2H,9H,10H)-one derivatives favored by buffering agent HEPES as a catalyst in ethyl alcohol. HEPES have a zwitterionic structure that drives successful interaction between reactants at near-neutral pH. This synthetic strategy also covers the advantages of one-pot multicomponent transformations, which will make this research work practical and economically feasible and provides foresight for sustainability.

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REFERENCES


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