GREEN SYNTHESIS OF BIOACTIVE 2-PHENylimidazo [4,5-f][1,10]-PHENANTHROLINE

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ABSTRACT:
An efficient and one pot method for smooth conversion of substituted aldehydes and 1,10-phenanthroline-5-dione into a range of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline have been synthesized in very good yield under solvent-free conditions by grinding 1,10-phenanthroline-5dione, aromatic aldehydes and ammonium acetate in the presence of [HBim] BF₄ ionic liquid as a catalyst as well as solvent. The ionic liquid can be recycled and reused several times. 2-phenylimidazo [4,5-f] [1,10]-phenanthroline was synthesized and tested for antibacterial effects against Bacillus Subtilis, Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa. The antibacterial screening of the synthesized compounds were performed in vitro by the filter paper disc diffusion method. The short reaction time, clean reaction, and easy workup make this protocol green and practically economical attractive and efficient.

KEYWORD:-2-phenylimidazo [4,5-f] [1,10]- phenanthroline, aldehydes, 1,10-phenanthroline-5-dione, ammonium acetate, antibacterial activity.

INTRODUCTION:-
2-phenylimidazo [4,5-f] [1,10]- phenanthroline possess synthetically challenging scaffold skeleton and is a basic structure of several synthetic drugs. The heterocyclic compounds with fused Imidazo-Phenanthroline ring system represent an important class of ligand used as a Convenient Modular Platform for the Preparation of Heteroleptic Cu(I) Photosensitizers. In addition, the substituted imidazole ring systems are substantially used in ionic liquids that have been given a new approach to “Green Chemistry”. Due to their great importance, many synthetic strategies have been developed. In 1882, Radziszewski and Japp reported the first synthesis of the imidazoles from 1, 2-dicarbonyl compound, various aldehydes and ammonia to obtain the imidazoles.²⁻³ The Ru(II) metal complexes of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline has been attracted considerable attention of chemist for many years, because their utilities in DNA structure prob⁵⁻⁶.

Many ammine complexes of ruthenium (II) tend to bind selectively to imine sites in bimolecules because of their nitrogen lone pairs that are available for metal ion coordination. Consequently, ruthenium complexes often selectively conjugate the histidyl nitrogen of imidazole on proteins and the N7 site on the imidazole ring of purine nucleotides. These heterocyclic structures forms the skeleton of natural alkaloids which act as
neuromuscular blocking agent, reversible inhibitors of the H⁺, K⁺, ATPase enzyme with a potent anti-secretory activity and sedative hypnotics of the nervous system. Literature survey shows that synthesis of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline has various routes like from 1,10-phenanthroline-5,6-dione with aldehyde in the presence of ammonium acetate in acetic acid and anhydrous ZnCl₂ mediated the formation of 2-(2-phenylimidazol-1-yl)-1H-imidazol-1-yl in methanol and molecular iodine. Most routes involve reaction of a 2-amino methyl pyridine with acylation followed by cyclization with phosphorus oxy chloride or polyphosphoric acid or thio cyclation followed by ring closure using DCC or mercuric salts. Imidazo-[1,5-a]-pyridines were also obtained from 2-cynopyridine by the Vilsmeir reaction or by reaction with Schiff bases in the presence of three steps from the diprydyl ketone, using nitriles and esters also reported by using potassium ferrocynide. However these methods require prolong and exotic reaction condition. Thus the development of a new method for the synthesis of imidazoles derivatives would be highly desirable. We have already reported the synthesis of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline at room temperature. But now we extend our work to study and find out the catalytic amount of ionic liquid used with respect to the isolated yield of the desired product and it’s antimicrobial activity. Initially, a systematic study was carried out for catalytic evaluation of complex for 2-phenylimidazo [4,5-f] [1,10]-phenanthroline, benzaldehyde and ammonium acetate (Table 1). The enhancement of mol% of [HBim]BF₄ enhance the yield of the product and reduce the reaction time (entry 1-5). The reaction went to completion in 10-30 minutes at room temperature with 10 mol% [HBim]BF₄. Accordingly, 10 mol% was sufficient to catalyze the reaction. As per shown in the Figure: rate enhancement with high yield was observed when higher molar ratios of ionic liquid were used. However, no product formation was observed in absence of [HBim]BF₄.

Table 1: Catalytic evaluation of [HBim]BF₄ for the synthesis of 3a

<table>
<thead>
<tr>
<th>Entry</th>
<th>[HBim]BF₄ (mol %)</th>
<th>Time (Sec)</th>
<th>Yield a,b (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>180</td>
<td>00</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>80</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>68</td>
<td>90</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>18</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>15</td>
<td>15</td>
<td>94</td>
</tr>
</tbody>
</table>

a: Reaction Condition; 1,10-phenanthroline-5,6-dione, (1mmol), benzaldehyde (1 mmol), ammonium acetate (2.5 mmol), RT Room temperature

b: Isolated yield after column chromatography
Material and Methods:

Synthesis of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline²⁷:

mixture of benzaldehyde(1mmol), 1,10-phenanthroline-5,6-dione, (1mmol), NH₄OAC(2.5mmol) and [HBim]BF₄ (10mmol) were ground together in a mortar with a pestle at room temperature for appropriate time as shown in table-1. Completion of reaction is confirmed by TLC the mixture was further purified by column chromatography by using methanol : benzene and recrystallised from methanol. Recently ionic liquid has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various organic transformation²⁸ offering the corresponding products in excellent yield with high selectivity.

Schem-1 Synthesis of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline

The mild Lewis acidity associated with ionic liquid enhanced its usage in organic synthesis to realize several organic transformation using stoichiometric levels to catalytic amount. Owing to numerous advantages associated with this eco-friendly element, ionic liquid has been explored as a powerful catalyst for various
During the course of our studies towards the development of new routes to the synthesis of biologically active heterocycles.

The ammonium acetate is acting as a nitrogen source for the formation of imines I. Due to the high selectivity the [HBim]BF₄ ionic liquid attached to the both carbonyl group of 1,10-phenanthroline give an intermediate II which cyclized to form product via intermediate III as mention in scheme-2. By getting this result, we have extended this protocol to a variety of aldehydes and summarized in Table 1. This protocol is rapid and efficient for the preparation of several 2-phenylimidazo [4,5-f] [1,10]-phenanthroline from both electrons efficient as well as electron deficient aromatic aldehydes. Electron-withdrawing groups enhance the rate of the reaction as compare to the electron-donating group.

![Schem-2 Possible mechanism of the synthesis of 3a-f](image)

Aliphatic aldehydes were also used as starting carbonyl compounds for the same reaction. The ortho and para substituents activate the aromatic ring of aldehydes and increase the rate of the reaction. While meta substitution requires somewhat greater time as compared to the o/p substituent’s. A nearly stiochiometric amount of ammonium acetate was used in the course of the reaction, whereas previously a many-fold excess of ammonium acetate was required. This is an additional advantage of the novel methodology. Here we report an easy procedure for synthesizing of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline catalyzed by inexpensive and nontoxic [HBim]BF₄ in the presence of ammonium acetate under solvent free condition with excellent yield and easy work up.
Table 1: Synthesis of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline 3a:

<table>
<thead>
<tr>
<th>Entry</th>
<th>Aldehyde</th>
<th>(^*)Product</th>
<th>Time (sec.)</th>
<th>(^b)Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>(\text{C}_6\text{H}_5\text{CHO})</td>
<td><img src="image" alt="Synthesis 3a" /></td>
<td>18</td>
<td>82</td>
</tr>
<tr>
<td>3b</td>
<td>(\text{C}_6\text{H}_4\text{CHO})</td>
<td><img src="image" alt="Synthesis 3b" /></td>
<td>23</td>
<td>89</td>
</tr>
<tr>
<td>3c</td>
<td>(\text{H}_3\text{COCHO})</td>
<td><img src="image" alt="Synthesis 3c" /></td>
<td>18</td>
<td>88</td>
</tr>
<tr>
<td>3d</td>
<td>(\text{O}_2\text{NCHO})</td>
<td><img src="image" alt="Synthesis 3d" /></td>
<td>12</td>
<td>82</td>
</tr>
<tr>
<td>3e</td>
<td>(\text{C}_6\text{H}_5\text{CHO})</td>
<td><img src="image" alt="Synthesis 3e" /></td>
<td>18</td>
<td>85</td>
</tr>
<tr>
<td>3f</td>
<td>(\text{H}_3\text{COCH(OCH}_3\text{)})</td>
<td><img src="image" alt="Synthesis 3f" /></td>
<td>20</td>
<td>89</td>
</tr>
</tbody>
</table>

\(^a\)Products were characterized by \(^1\text{H}\) NMR, \(^{13}\text{C}\) NMR, Mass, elemental analysis and comparison with authentic sample, \(^b\)Isolated yield after column chromatography.

**Result and discussion:**

In conclusion, [HBim]BF\(_4\) was found to be a mild and effective catalyst for the formation of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline in excellent yields. The uses of this inexpensive and easily available catalyst under solvent-free conditions make this protocol green and economically attractive. The simple work-up procedure, mild reaction conditions, selectivity, and very good yields make our methodology a valid contribution to the existing processes in the field of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline derivatives synthesis.
The formation of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline are confirmed by spectral analysis. The IR spectra of 4-N,N-dimethyl-2-phenylimidazo [4,5-f] [1,10]-phenanthroline shows absorption at 1687,2257 and 3355 cm⁻¹ corresponding to the C=N, NH and tertiary amino group respectively. The ¹H NMR spectra shows 1H(s) δ=2.0, for NH gr, 6H(s) δ=3.00 for methyl group,4H(d) δ=6.65-7.30 for aromatic benzene, 4H(d) δ=8.00-8.81,2(H) δ=7.26 mass 207(M⁺),185,165,127. These result shows the confirmation of the formation 4-N,N-dimethyl-2-phenylimidazo [4,5-f] [1,10]-phenanthroline (3e).

EXPERIMENTAL:

General procedure for the synthesis of 2-phenylimidazo [4,5-f] [1,10]-phenanthroline (3a-f):

A mixture of benzaldehyde (1mmol), 1,10-phenanthroline 5,6-dione (1mmol), ammonium acetate (20mmol) and [HBim]BF₄ (10mmol) were grind together in a mortar with pestle at room temperature for appropriate time Table-1 after completion of reaction confirmed by TLC. The crude was further purified by column chromatography by using petroleum ether: ethyl acetate (9:1) eluent and get the corresponding 2-phenylimidazo [4,5-f] [1,10]-phenanthroline. The products 3(a-f) were confirmed by comparison with authentic sample, ¹H NMR, ¹³C NMR, mass, elemental analysis and melting points.

ANTIMICROBIAL ACTIVITY

The antibacterial activities of the synthesized compounds 2-phenylimidazo [4,5-f] [1,10]-phenanthroline were studied against four bacteria, viz. Bacillus subtilis (G+), Escherichia coli (G–), Staphylococcus aureus (G+) and Pseudomonas aeruginosa (G–). For the detection of antibacterial activities, the filter paper discs diffusion method was used²⁹. Streptomycin sulphate was used as positive control. Nutrient agar (NA) was used as basal medium for test bacteria. The discs were prepared by impregnating them in methanol solution of each sample (1 mg/1 mL). Each culture was prepared to a turbidity equivalent to McFarland and spread on the test tube. The paper disc containing the compound was placed on the agar surface previously inoculated with suspension of each microbes to be tested. All determinations were made in duplicate. Inhibition diameter was determined after incubation at 37°C ± 1 for 24 h. The antimicrobial activity was indicated by the presence of the clear inhibition zones around each disc.

The antibacterial activity of compounds (3d) and (3e) has been assayed at the concentration 1000 μg/mL against four human pathogenic bacteria. Among them two were gram-positive and the other two were gram negative. The inhibitory effect of compounds (3d) and (3e) against these organisms are given in Table 2. The screening results indicate that only compound (3d) was active against a gram-negative bacteria, Escherichia coli with a mean zone of inhibition 12.5 ± 0.3 mm (table 2).

Determination of the minimum inhibitory concentration (MIC):

The active sample in the disc diffusion method was then tested for its activity by the serial dilution method to determine the minimum inhibition concentration (MIC-value). The MIC value obtained for 2-phenylimidazo [4,5-f] [1,10]-phenanthroline was 1000 μg/mL against Escherichia coli.
Fig 02:- Diameter of the zone of inhibition (mm)

Table 2. Antibacterial screening for the compounds (3d) and (3e)

<table>
<thead>
<tr>
<th>Organism</th>
<th>Chalcones</th>
<th>2-phenylimidazo [4,5-j] [1,10]-phenanthroline</th>
<th>Streptomycin sulphate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacillus subtilis</td>
<td>-</td>
<td>-</td>
<td>22.0 ± 0.3</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>-</td>
<td>-</td>
<td>22.5 ± 0.7</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>-</td>
<td>12.5 ± 0.3</td>
<td>22.0 ± 0.0</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>-</td>
<td>-</td>
<td>22.0 ± 0.0</td>
</tr>
</tbody>
</table>

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References:


