RESEARCH PLAN PROPOSAL

Theoretical and experimental investigations of cycloaddition reactions of imidazo[1,2-a]pyridines and related heterocycles

For registration to the degree of
Doctor of Philosophy

IN THE FACULTY OF SCIENCE

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**INTRODUCTION**

Heterocycles form one of the most important and well investigated classes of organic molecules owing to their occurrence in living organisms and a wide range of biological activity. The key role in heterocyclic chemistry belongs to heteroaromatic structures, in particular to five- and six-membered rings and their fused-ring derivatives. It is well known that the difference in chemical behavior between five- and six-membered rings is accounted for by different aromaticities and different $\pi$-excessive or $\pi$-deficient characters of their electronic structures e.g. pyrrole and pyridine.\(^1\)

Imidazo[1,2-$a$]pyridines or 1-azaindolizines (1) and the related imidazo[1,2-$a$]pyrimidines (2) have received significant attention from the pharmaceutical industry owing to their interesting biological activities displayed over a broad range of therapeutic classes,\(^2\) showing antiulcer,\(^3\) antiviral,\(^4-6\) antifungal\(^7\) and anti-inflammatory\(^8\) activities.

![Figure 1](image-url)

1. $X = \text{CH}$
2. $X = \text{N}$

**Figure 1.**
The most commonly used method for the synthesis of imidazo[1,2-\(a\)]pyridines and imidazo[1,2-\(a\)]pyrimidines involves cyclocondensation of 2-aminopyridines or 2-aminopyrimidines with \(\alpha\)-halocarbonyl compounds.\(^6, 9-14\) Although several other methods of synthesis have also been reported,\(^15-21\) they are found to be more cumbersome.

Like indolizine,\(^1\) imidazo[1,2-\(a\)]pyridine and imidazo[1,2-\(a\)]pyrimidine are composed of a \(\pi\)-excessive five-membered ring and a \(\pi\)-deficient pyridine ring with only one bridgehead nitrogen. Literature survey reveals that though a number of \([8+2]\) cycloaddition reactions of indolizine with a variety of alkenes and alkynes have been accomplished successfully,\(^1\) no \([2+4]\) cycloaddition has been reported so far. In contrast to indolizine,\(^22-35\) the reactivity of imidazo[1,2-\(a\)]pyridine and imidazo[1,2-\(a\)]pyrimidine has been investigated experimentally or theoretically sparsely.

The presence of an additional pyridine type nitrogen (N1) in the five-membered ring of imidazo[1,2-\(a\)]pyridine and imidazo[1,2-\(a\)]pyrimidine may be expected to decrease the electron rich character of this ring, as its own lone-pair is not involved in the delocalisation. Moreover, the presence of N1 in the five-membered ring offers the possibility of decreasing the electron-density through its alkylation or coordination to the Lewis acid such as AlCl\(_3\).
**REVIEW OF LITERATURE**

- **International Status**

  Literature survey reveals that only one [8+2] cycloaddition of imidazo[1,2-\(a\)]pyridine and imidazo[1,2-\(a\)]pyrimidine has been reported so far. Cossio and coworkers\(^{36}\) reported the experimental and theoretical results of [8+2] cycloadditions of imidazo[1,2-\(a\)]pyridines and imidazo[1,2-\(a\)]pyrimidines with benzyne. The [8+2] cycloaddition steps are essentially barrierless and the aromatization steps occur via highly synchronous aromatic transition structures (Scheme 1).

![Scheme 1](image)

a. X = CH
b. X = N

- **National Status**

  According to our knowledge, no other research group is working on these heterocyclic systems.
JUSTIFICATION AND RELEVANCE:

Theoretical studies will be used for molecular modeling of imidazo[1,2-a]pyridine and imidazo[1,2-a]pyrimidine that is, its reactivity will be tuned by appropriate substitution.

Synthesis of new heterocyclic compounds which may show interesting bioactivities.

Identification of these new products by spectral techniques will enrich the existing knowledge in the chemistry.

OBJECTIVES

1. Theoretical investigation of dienophilic reactivity of C(2)=C(3) functionality present in imidazo[1,2-a]pyridine and imidazo[1,2-a]pyrimidine and its tuning by introducing various substituent groups such as NO₂, CF₃, CH₃, etc. in the five- or six-membered rings.

2. Effect of N1 alkylation or its coordination to a Lewis-acid on the dienophilic reactivity of C(2)=C(3) functionality.

3. Theoretical investigation of dienophilic reactivity of C(2)=C(3) towards reverse electron-demand Diels-Alder reaction using electron-deficient heterodienes.
4. Normal electron-demand (NED) and reverse electron-demand (RED) Diels-Alder reactions of substituted imidazo[1,2-a]pyridines and imidazo[1,2-a]pyrimidines experimentally.


❖ HYPOTHESIS

The proposed research work is based on the concept of [4+2] and [8+2] cycloaddition reactions, which are symmetry allowed according to Woodward-Hoffmann rule.

❖ PLAN OF WORK AND METHODOLOGY

1. Determination of activation barriers and energies of reactions for normal electron-demand (NED) and reverse electron-demand (RED) Diels-Alder reactions of imidazo[1,2-a]pyridine and its following derivatives:
Scheme 2. Theoretical investigation of NED DA reactions

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<th>2/b</th>
<th>3/c</th>
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<th>5/e</th>
<th>6/f</th>
<th>7/g</th>
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<th>9/i</th>
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<tr>
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<td>AlCl_3</td>
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</tr>
</tbody>
</table>

Scheme 3. Theoretical investigation of RED DA reactions

2. Determination of activation barriers and energies of reactions for the DA reactions of imidazo[1,2-a]pyrimidines.

On the basis of the theoretical results, those substituted imidazo[1,2-\(a\)]pyridines and imidazo[1,2-\(a\)]pyrimidines will be synthesized which are expected to undergo DA reactions.

\[
\text{Scheme 4.}
\]

4. Normal electron-demand (NED) Diels-Alder reactions of imidazo[1,2-\(a\)]pyridines and imidazo[1,2-\(a\)]pyrimidines will be carried out with following 1,3-dienes-

\[
\text{Figure 2.}
\]

5. Reverse electron-demand (RED) Diels-Alder reactions of unsubstituted and substituted imidazo[1,2-\(a\)]pyridines and imidazo[1,2-\(a\)]pyrimidines will be carried out with the following orthoquinones-
a. Tetrachloro-o-benzoquinone

![Tetrachloro-o-benzoquinone](image)

b. Naphthoquinone

![Naphthoquinone](image)

c. Penanthrenequinone

![Penanthrenequinone](image)

d. 3,5-Di(tert-butyl)-o-benzoquinone

![3,5-Di(tert-butyl)-o-benzoquinone](image)

Figure 3.

6. Stereoselectivity and regioselectivity in the above reactions would be investigated theoretically and experimentally.


❖ **YEARWISE PLAN OF WORK**

- **First year:** Theoretical and experimental work on imidazo[1,2-a]pyridines.
- **Second year:** Theoretical and experimental work on imidazo[1,2-a]pyrimidines.
- **Third year:** Compilation and publication of the research work.

❖ **PLACE OF WORK AND FACILITIES AVAILABLE**

Department of Chemistry, IIS University, Jaipur. A modern well equipped laboratory, with modest instruments is available.

❖ **LIMITATION AND ALTERNATIVE PLAN OF STUDY**

The non-availability of multinuclear NMR spectrometer is the main limitation. We shall try to take the help of the institutions where this instrument is available.
REFERENCES


