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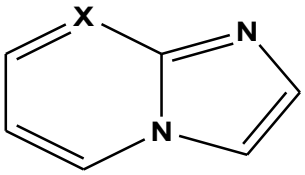
TOPIC: Theoretical and experimental investigations of cycloaddition reactions of imidazo[1,2-*a*]pyridines and related heterocycles

❖ 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 π-excessive or π-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.



1. X = CH
2 .X = 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-aminopyimidines with α-halocarbonyl compounds.[6, 9-14] Although several other methods of synthesis have also been reported,[15-21] they are found to be more cumbersome.

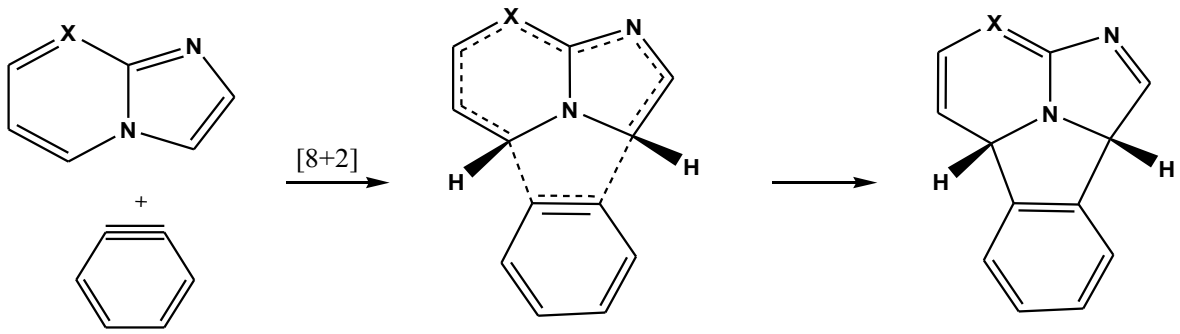
Like indolizine,[1] imidazo[1,2-*a*]pyridine and imidazo[1,2-*a*]pyrimidine are composed of a π-excessive five-membered ring and a π-deficient pyridine ring with only one bridgehead nitrogen. Literature survey reveals that though a number of [8+2] cycloaddition reactions of indolizine with a variety 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**).



a. X = CH
b. X = N

Scheme 1.

➢ 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 NO_2, CF_3, CH_3, 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.

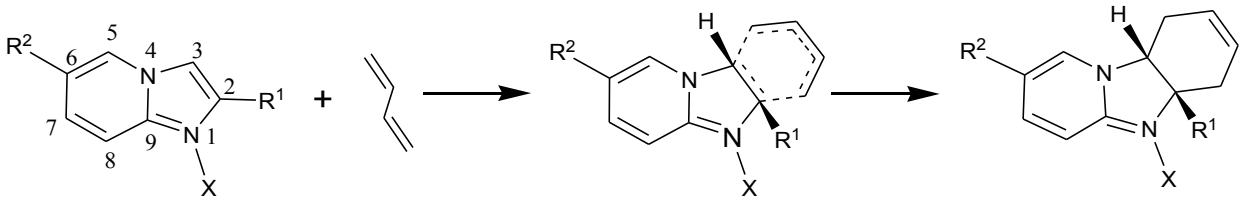
5. Investigation of [8+2] cycloadditions of imidazo[1,2-*a*]pyridines theoretically and experimentally.

❖ 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

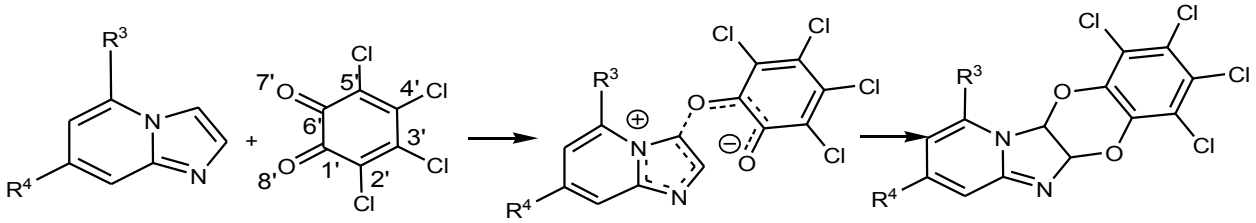
1. Determination of activation barriers and energies of reactions for normal electron-demand (NED) and reverse electron-demand (RED) Diels-Alder reactions of imidazo[1,2-*a*]pyridine and its following derivatives:



1 **1,3-butadiene** **TS** **Pr**

Reaction no./1	**1/a**	**2/b**	**3/c**	**4/d**	**5/e**	**6/f**	**7/g**	**8/h**	**9/i**	**10/j**	**11/k**
R^1	H	CF_3	CH_3	NO_2	H	H	H	H	H	H	H
R^2	H	H	H	H	CF_3	CH_3	NO_2	H	NO_2	H	H
X	-	-	-	-	-	-	-	$AlCl_3$	$AlCl_3$	CH_3	CH_2Ph

Scheme 2. Theoretical investigation of NED DA reactions



1 **TCQ** **TS** **Pr**

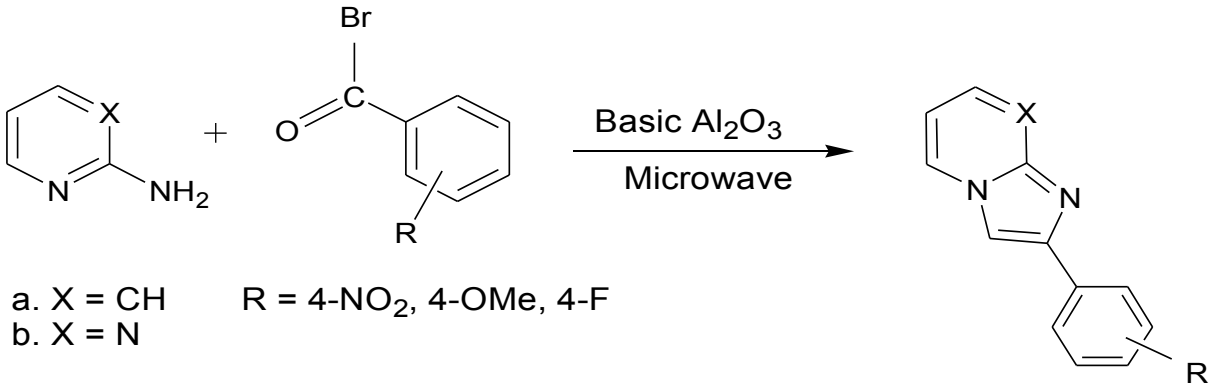
Reaction no./1	**12/l**	**13/m**	**14/n**	**15/0**	**16/p**
R^3	H	NH_2	OMe	H	H
R^4	H	H	H	NH_2	Ome

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.

3. Synthesis of appropriately substituted imidazo[1,2-*a*]pyridines and 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.



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-

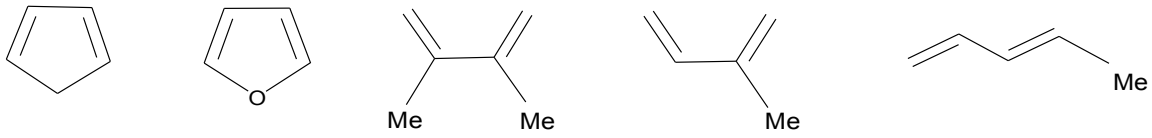
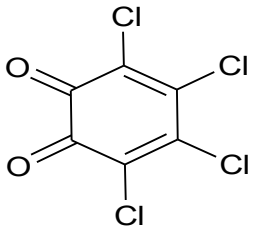


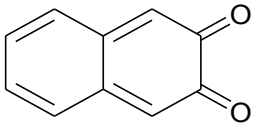
Figure 2.

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-

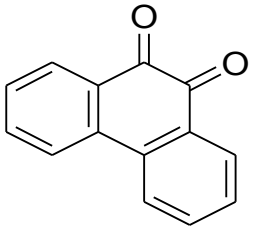
   a. Tetrachloro-o-benzoquinone



b. Naphthoquinone



c. Penanthrenequinone



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

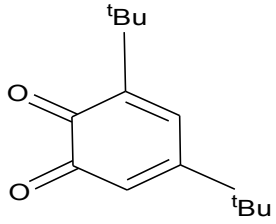


Figure 3.

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

7. Investigation of [8+2] cycloadditions of imidazo[1,2-*a*]pyridines theoretically and experimentally.

8. Microwave assisted tandem synthesis of imidazo[1,2-*a*]pyridines and their [8+2] cycloaddition.

❖ 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.

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