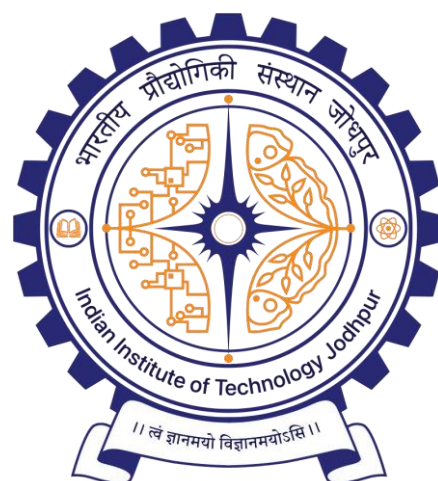


Visible Light Driven Alkylation and Cascade Annulation Using *N*-(acyloxy)phthalimides and Aryl Diazo Esters

A Thesis submitted by
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5. General Conclusion

5.1 Concluding Remarks on Each Chapter

This thesis showcases the development of visible-light-mediated methodologies for accessing structurally diverse and biologically relevant compounds using sustainable and efficient approaches. The research addresses key challenges in radical chemistry and carbene-mediated transformations by introducing green, metal-free methods for heterocycle synthesis via cascade annulation and modification with direct alkylation. The thesis is organized into five chapters: Introduction (**Chapter 1**), Three Experimental Works (**Chapters 2–4**), and Conclusion (**Chapter 5**). The major findings of each chapter are summarized below.

Chapter 1: Introduction

- i) We have introduced visible-light photochemistry and briefly discussed the fundamentals and the significance of tools like photo-redox catalysis, electron donor-acceptor (EDA) complexes, and direct photolysis in organic synthesis.
- ii) Then, we focus on the importance and alkylation of *N*-Heterocycles with different alkylating reagents. After showing challenges in existing synthetic methodologies that emphasize the need for robust, bench-stable, and abundant alkylating reagents.
- iii) Introduction of NHPI esters for direct alkylation and cascade reactions. Then, visible-light-mediated transformations of diazo compounds to synthesize biologically relevant molecules.
- iv) At last, we have provided an overview of this thesis and showed how we achieved our goals in different chapters.

Chapter 2: *N*-Heterocycle Formation via Radical (4+2) Annulation for Tetrahydroquinolines

- i) We have solved a regioselectivity issue by designing an NHPI ester. This undergoes a visible light EDA-complex-promoted (4+2) radical annulation with *N*-substituted maleimides.
- ii) This photocatalyst and oxidant-free reaction give *N*-Heterocycles exhibited a broad scope, regioselectivity, scalability, and functional group tolerance.
- iii) We also provide mechanistic insights, supported by DFT calculations and radical trapping experiments, which reveal the formation of tetrahydroquinolines through a stepwise radical pathway.

This EDA complex strategy may be applied to the assembly of other fused heterocyclic frameworks using other radical acceptors or NHPI ester substrates. This would make the improved method applicable to a wider spectrum of biologically relevant molecules. A further possible plan will be to investigate the preparation of asymmetric versions of this cascade by the addition of chiral amines or auxiliaries to provide access to optically active tetrahydroquinoline derivatives, which have potential applications in the pharmaceutical industry. Furthermore, the developed strategy could be used for late-stage modification of complex molecular systems, such as natural products or medicinal compounds bearing maleimide or related motifs, in drug discovery processes to access new analogs of valuable compounds for biological studies. More comprehensive investigations, including computational and kinetic studies, might also be performed to reveal novel radical cascade processes and aid in the design of more sophisticated multicomponent reactions.

Chapter 3: Direct Csp³-H Alkylation of 3,4-Dihydroquinoxalin-2-ones

- We have achieved metal-free organic photoredox-catalyzed direct alkylation of 3,4-dihydroquinoxalin-2-ones using NHPI esters as alkyl radical surrogates.
- This method provides excellent yields, functional group tolerance, and compatibility with various NHPI esters (primary, secondary, tertiary, and sterically hindered) to give alkylated 3,4-dihydroquinoxalin-2-ones.
- Detailed mechanistic studies clarified the role of photoredox catalysis in facilitating radical generation and coupling.

Similarly, libraries of alkylated analogs can be developed for drug discovery and biological screening, with new therapeutic candidates as possible results. A further outlook would be the combination of this C-H alkylation with other functionalization methods, including arylation or amination, with the aim of allowing sequential or even tandem functionalization to prepare more complex molecules in fewer steps. In summary, new organic or metal-free photocatalysts may bring about better reaction efficiency, selectivity, or greenness, while mechanistic studies may provide more insight and novelty for future photoredox systems to design.

Chapter 4: N-alkylation of (Aza)uracils with Aryl Diazo Esters

- Here, we develop green, sustainable N-alkylation of azauracils and uracils using α -diazo esters under visible-light irradiation.
- This methodology operates under catalyst- and additive-free conditions, offering both insertion and three-component coupling in cyclic ethers with a high efficiency.
- This divergent approach allowed the modification of natural products and pharmaceuticals, highlighting their potential for biologically relevant applications.

The application of this method to three-component coupling reactions (with cyclic ethers) can be examined by testing other nucleophilic solvents or additives, which may allow the emergence of new classes of N-alkylated heterocycles. A further interesting trend is the extension of this strategy to nucleoside analogs, which might be useful for preparing modified nucleotides for drug design and chemical biology. Because the reaction is water compatible, future work could try to further investigate fully aqueous or biocompatible conditions, which would then make the protocol interesting in light of the late-stage functionalization of biomolecules.

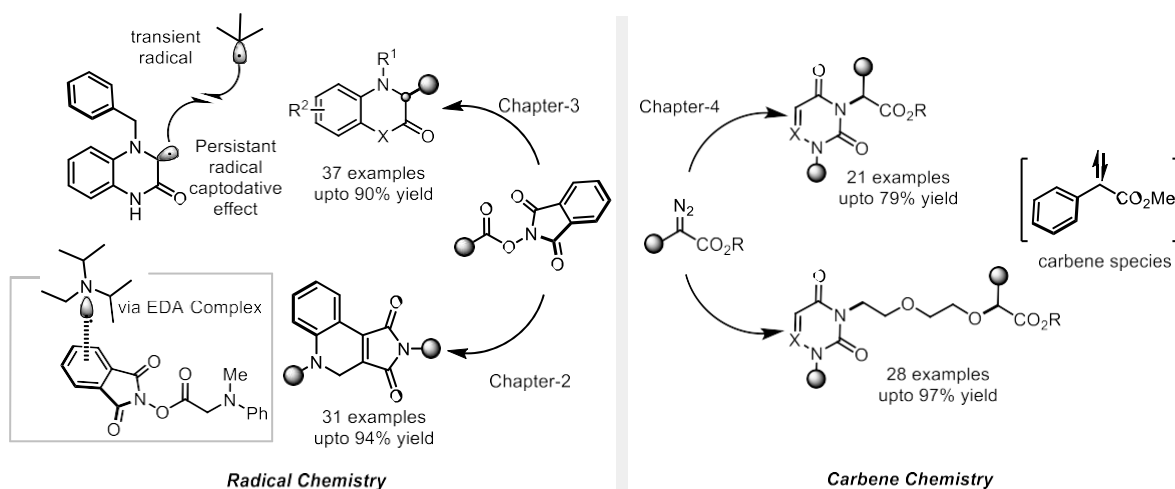


Fig 5.1 Summary of the Experimental Work.

5.2 Final Remarks

This thesis explores alkylation and alkylative cascade reactions, highlighting the power of visible-light-mediated processes to develop sustainable, scalable reactions to access high-value organic compounds. In the first chapter, we describe in detail a new, photocatalyst-free approach to the formation of N-heterocycles, where we use the EDA complex to add an NHPI ester selective to yield tetrahydroquinolines, a new derivation from the literature. Chapter two demonstrates the utility of organic photocatalysis for targeting the notoriously challenging C-H bonds of organic compounds, emphasizing C(sp³)-H bonds. Using this cheap, readily available rose bengal photocatalyst, we could alkylate 3,4-dihydroquinoxalin-2-ones and extend C-H functionalization to new territories. The third chapter introduces the functionalization of azauracils and uracil without additives, which is an adventurous development. Combining the concepts of EDA complex formation, photocatalysis, and direct photolysis, this work illuminates new strategies for heterocycle synthesis, direct C(sp³)-H functionalization, and late-stage diversification of bioactive compounds. This work illustrates, with insightful mechanistic studies and a diverse scope, the remarkable progress in sustainable organic synthesis and lays the groundwork for continued exploration and development in the field of chemistry.

In summary, the strategies and methodology advanced in this thesis hold the potential to spur new research advancement in green chemistry and organic synthesis in the future. New, more sustainable approaches to functionalizing complex organic molecules are becoming possible when this is critically needed, driven by the potential of employing visible light and photoredox catalysis to effect these transformations. These novel alkylation and heterocycle formation methods were anticipated to revolutionize conventional synthetic pathways and potentially impact the development of drugs, materials, and bioactive compounds. Its impressive biocompatibilities may soon be augmented to span a wider array of biochemistries, paving the way for applications in multiple fields, ranging from drug discovery to material science.

“NHPI esters serve as reliable precursors for forming N-heterocycles, resulting in a highly regioselective synthesis of tetrahydroquinolines via photocatalyzed reactions. In contrast, aryl diazo esters are utilized for N-alkylation, enabling these heterocycles’ functionalization through nitrogen alkylation. Collectively, these strategies provide a powerful platform for synthesizing and diversifying complex heterocyclic species and an enabling strategy to functionalize notoriously difficult C(sp³)-H bonds.”