EXPLORATION OF OXIDATIVE COUPLING AND MULTI-COMPONENT REACTIONS FOR THE SYNTHESIS OF FUSED AROMATICS AND HETEROCYCLIC COMPOUNDS

VIJAY

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by

VIJAY

DEPARTMENT OF CHEMISTRY

Submitted

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Dedicated to my beloved parents

CERTIFICATE

This is to certify that the thesis entitled, **"Exploration of Oxidative Coupling and Multi-Component Reactions for the Synthesis of Fused Aromatics and Heterocyclic Compounds"**, being submitted by **Mr. Vijay** to the Indian Institute of Technology Delhi for the award of the degree of **Doctor of Philosophy** in Chemistry is a record of bonafideresearch work carried out by him. Mr. Vijay worked under my guidance and supervision and has fulfilled the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard.

The results contained in this dissertation have not been submitted in part or full to any other University or Institute for the award of any degree or diploma.

(**Dr. Ravi P. Singh**)
Associate Professor,
Department of Chemistry
Indian Institute of Technology Delhi
New Delhi-110016

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ABSTRACT

The thesis entitled **"Exploration of Oxidative Coupling and Multi-Component Reactions for the Synthesis of Fused Aromatics and Heterocyclic Compounds"**deals with the development of new methodology for the synthesis of extended *л*-conjugated aromatic compounds and stereoselective reactions for the synthesis of spatially organize functionalized scaffolds. Fused aromatic compounds are useful in material sciences as well as in biological sciences. Different stereoisomers can show varied response towards human senses such as smell and taste, behaviour of insects and most importantly pharmacological activity in human body. Thus, it is very important to selectively synthesize the desired diastereomer and enantiomer through meticulous choice of catalysts and reaction conditions. We have developed CAN-mediated oxidative coupling for fused aromatics, and the diastereoselective MCR and organocatalysed asymmetric vinylogous Michael reactions for synthesis of heterocyclic compounds.

This thesis is divided into five chapters. **Chapter 1** is introduction about various types of oxidative coupling reactions employed in C-C bond formation with main emphasis on dehydrogenative coupling of aromatic compounds. It also preludes stereoselective multicomponent reactions which includesorganocatalysis, their activation modes such as covalent and non-covalent organocatalysis.

Chapter 2 describes inter/intramolecular oxidative coupling of aromatic compounds for the synthesis of phenanthrene derivatives. Phenanthrene ring is an important core of biologically active natural alkaloids such as phenathroindolizidine and phenanthroquinolizidine. Various oxidants have been reported for the preparation of phenanthrene ring, unfortunately most of them are toxic in nature, low yielding and poor substrate scope. Here, a methodology for the construction of 9-substituted phenanthrenes derivatives *via* intramolecular oxidative dehydrogenative coupling of 2,3-diphenyl acryl compounds using oxidant cerium(IV) ammonium nitrate at ambient temperature has been developed. This protocol is easy to execute, environmental friendly, and cost effective.

In **chapter 3**, intramolecular oxidative cyclodehydrogenation of the aromatic compounds for the synthesis of triphenylenes and their hetreoanalogous have beendescribed. Triphenylene is an important core of discotic liquid crystals which have wide applications in

making electronic appliances. Most of the literature reports are limited for the synthesis of triphenylene derivatives and have not been much explored for the synthesis of *N*-heterocyclic fused aromatic compounds. It has been a challenge to achieve fused heteroaromatics by direct oxidative coupling of their corresponding precursors which we have tried to overcome. A CAN-mediated oxidative cyclodehydrogenation of *o*-terphenyls for the synthesis of alkoxy substituted triphenylens have been realized. This methodology was further explored to achieve *N*-heterocyclic fused heteroaromatics such as imidazole fused triphenylenes, pyrazine fused triphenylene and phenanthro[9,10-*d*]pyrazines.

Chapter 4 describes stereoselective multi-component reaction for the synthesis of heterocyclic 2-amino-4*H*-chromene derivatives. Due to biological importance of such moieties, earlier numerous other heterocyclic rings such as dimedones, indoles, pyrazolones etc. have been incorporated into 2-amino-4*H*-chromene either in one-pot or in step-wise manner. In multicomponent reaction, more than two components react in one-pot so it is always a challenge to control the regio- and stereo-chemical outcomes of the reaction. A novel methodology to for the synthesis of 2-amino-4-(2-furanone)-4*H*-chromene-3-carbonitriles has been developed. In this protocol, salicylaldehydes, malononitriles and butenolides reacted all together in one-pot in the presence of base sodium *tert*-butoxide to afford 2-amino-4-(2-furanone)-4*H*-chromene-3-carbonitriles. Herein, we have achieved chemoselectivity and regioselectivity along with diastereoselectivity.

Chapter 5 describes organcatalytic diastereo- and enantioselective vinylogous Michael addition of *β,γ*-butenolide with various 2-iminochromenes. Chiral *γ*-butenolide and their derivatives are present in numerous natural products and are important building blocks for the synthesis of biologically active compounds. We have demonstrated a quinine-derived organocatalysed *syn*-selective asymmetric vinylogous Michael reaction of *α*-Angelica lactone to 2-iminochromenes. Incorporation of butenolide scaffold in 2-amino-4*H*-chromene will allow to access to highly functionalized chiral cores, wchich might have higher bioactivities than the parent scaffolds.

सार

हकदार थीसिस मे "फ़्यूज़्ड एरोमेटिक्स और हेटेरोसाईक्लिक यौगिकों के संश्लेषण के लिए ऑक्सीडेटिव युग्मन और बहु-घटक प्रतिक्रियाओं की खोज" विस्तारित *π*-संयुग्मित एरोमैटिक यौगिकों के संश्लेषण के लिए नई कार्यप्रणाली के विकास के साथ और स्थानिक रूप से व्यवस्थित स्कैफोल्डस के संश्लेषण के लिए स्टिरियोसेलेक्टिव प्रतिक्रियाओं की चर्चा की गई है। फ्यूज्ड एरोमैटिक यौगिक भौतिक विज्ञान के साथ-साथ जैविक विज्ञान में भी उपयोगी हैं। अलग-अलग स्टीरियोआइसोमर मानव इंद्रियों जैसे गंध और स्वाद, कीड़े के व्यवहार और मानव शरीर में सबसे महत्वपूर्ण औषधीय गतिविधि के प्रति विभिन्न प्रतिक्रिया दिखा सकते हैं। इस प्रकार, उत्प्रेरक और प्रतिक्रिया स्थितियों के सावधानीपूर्वक विकल्प के माध्यम से वांछित डाइस्टीरियोमर और इनानसीयोमर को चुनिंदा रूप से संश्लेषित करना बहुत महत्वपूर्ण है। हमने फ्यूज़्ड एरोमेटिक्स के लिए CAN-मध्यस्थता ऑक्सीडेटिव युग्मन विकसित किया है, और डायस्टेरोसेलेक्टिव MCR और ओर्गेनो-केटेलाईज़्ड असिमेट्रिक विनाइलोगस माइकल अभिक्रियाएँ हेट्रोसाइक्लिक यौगिकों के संश्लेषण के लिए की हैं।

यह थीसिस पाँच अध्यायों में विभाजित है। **अध्याय 1** विभिन्न प्रकार के ऑक्सीडेटिव युग्मन प्रतिक्रियाओं के बारे में बता रहा है, जो C-C बॉन्ड गठन में एरोमैटिक यौगिकों के निर्जलीकरणीय युग्मन पर मुख्य जोर देते हैं। यह स्टिरियोसेलेक्टिव मल्टीकोम्पोनेंट प्रतिक्रियाओं को भी शामिल करता है जिसमे ओर्गेनोकैटेलिसिस, उनके सक्रियण तरीके जैसे सहसंयोजक और गैर-सहसंयोजक ओर्गेनोकैटेलिसिस शामिल हैं।

अध्याय 2 में फेनानथ्रिन डेरीवेटिव के संश्लेषण के लिए एरोमैटिक यौगिकों के इंटर/इंट्रामोलिक्युलर ऑक्सीडेटिव युग्मन का वर्णन किया गया है। फेनानथ्रिन रिंग फेनथ्रोइंडोलिज़िडीन और फेनांथ्रोक्विनोलिज़िडिन जैसे जैविक रूप से सक्रिय प्राकृतिक अल्कलॉइड का एक महत्वपूर्ण कोर है। फेनानथ्रिन रिंग के संश्लेषण के लिए विभिन्न ऑक्सीडेंट्स की सूचना दी गई है, उनमें से ज्यादातर प्रकृति में विषाक्त हैं, कम उपज और खराब सब्सट्रेट गुंजाइश हैं। यहां, परिवेशी तापमान के लिए ऑक्सीडेंट सेरियम(IV) अमोनियम नाइट्रेट का उपयोग करके 2,3-डायफिनाइल एक्राइल यौगिकों के इंट्रामोलिक्युलर ऑक्सीडेटिव निर्जलीकरणीय युग्मन के माध्यम से 9-प्रतिस्थापित फेनानथ्रिन डेरिवेटिव के निर्माण की एक पद्धति विकसित की गई है। इस प्रोटोकॉल को निष्पादित करना आसान है, पर्यावरण के अनुकूल, और लागत प्रभावी है।

अध्याय 3 में, ट्राइफिनाइल्स के संश्लेषण के लिए एरोमैटिक यौगिकों के इंट्रामोलिक्युलर ऑक्सीडेटिव साइक्लोडिहाइड्रोज़िनेशन और उनके हेट्रोएनालॉग्स का वर्णन किया गया है। ट्राइफिनाइलीन एक महत्वपूर्ण कोर है डिस्कोटिक लिक्विड क्रिस्टल, जिसका इलेक्ट्रॉनिक उपकरणों को बनाने में व्यापक अनुप्रयोग हैं।
साहित्य की अधिकांश रिपोर्टें ट्राइफिनाइलीन डेरिवेटिव के संश्लेषण के लिए सीमित हैं और *N*-हेटेरोसायक्लिक फ्यूज एरोमैटिक यौगिकों के संश्लेषण के लिए बहुत अधिक नहीं पता लगाया गया है। यह उनके संबंधित अग्रद्रूतों के प्रत्यक्ष ऑक्सीडेटिव युग्मन द्वारा फ्यूजड हेटेरोएरोमैटिक्स को प्राप्त करने के लिए एक चुनौती है जिसे हमने दूर करने का प्रयास किया है। अल्कॉक्सी के प्रतिस्थापन के लिए o-टरफिनाइल्स के CAN-मध्यस्थता ऑक्सीडेटिव साइक्लोडिहाइड्रोजिनेशन को महसूस किया जा सकता है। इस पद्धति को आगे *N*-हेटेरोसायक्लिक फ़्यूज़्ड हेटेरोएरोमैटिक्स जैसे कि इमीडाजोल फ्यूजड ट्राइफिनाइलीन, पाइराजिन फ़्यूज़्ड ट्राइफिनाइलीन और फेनांथ्रो[9,10-*d*]पाइरेज़िन को प्राप्त करने के लिए खोजा गया था।

अध्याय 4 में विषमलैंगिक 2-अमीनो-4*H*-क्रोमिन डेरिवेटिव के संश्लेषण के लिए स्टीरियोसेलेक्टिव-मल्टीकंपोनेंट प्रतिक्रिया का वर्णन किया गया है। इस तरह के मोएटीज के जैविक महत्व के कारण, पहले कई अन्य हेट्रोसाइक्लिक रिंग जैसे डाइमेडोन्स, इंडोल्स, पाइरोजोलोन्स आदि को 2-एमिनो-4*H*-क्रोमिन में एक-पॉट में या चरण-वार तरीके से शामिल किया गया है। मल्टीकंपोनेंट प्रतिक्रिया में, दो से अधिक घटक एक-पॉट में प्रतिक्रिया करते हैं, इसलिए यह प्रतिक्रिया के रिजिओ- और स्टीरियो-केमिकल परिणामों को नियंत्रित करने के लिए हमेशा एक चुनौती होती है। 2-अमीनो-4-(फ्युरेन-2-आइल)-4*H*-क्रोमिन-3-कार्बोनाइट्राइल के संश्लेषण के लिए एक नॉवेल पद्धति विकसित की गई है। इस प्रोटोकॉल में, सैलिसिलेडिहाइड, मैलोनोनाइट्राइल्स और ब्यूटेनोलाइड्स ने बेस सोडियम टर्ट-ब्यूटॉक्साइड की उपस्थिति में एक साथ एक-पॉट में प्रतिक्रिया ने 2-अमीनो-4-(फ्युरेन-2-आइल)-4*H*-क्रोमिन-3-कार्बोनिट्राइल दिया । इस प्रकार, हमने डाइस्टीरियोसेलेक्टिविटी के साथ-साथ कीमोसेलेक्टिविटी और रिजिओसेलेक्टिविटी प्राप्त की है।

अध्याय 5 में विभिन्न 2-इमिनोक्रोमीन्स के साथ ऑर्गेनाकैटलिटिक डाइस्टीरियो- और इनानसीयोसेलेक्टिव विनाइलोगस माइकल *β*,*γ*-ब्यूटेनोलाइड का वर्णन किया गया है। काइरल *γ*-ब्यूटेनोलाइड और उनके डेरिवेटिव कई प्राकृतिक उत्पादों में मौजूद हैं और जैविक रूप से सक्रिय

यौगिकों के संश्लेषण के लिए महत्वपूर्ण निर्माण ब्लॉक हैं। हमने *α*-एंजेलिका लैक्टोन से 2-इमिनोक्रोमीन के लिए एक कुनीन-व्युत्पन्न ओर्गेनोकेटेलाईज़ड *syn*-चयनात्मक असममित विनाइलोगस माइकल प्रतिक्रिया का प्रदर्शन किया है। 2-अमीनो-4*H*-क्रोमीन में ब्यूटेनोलाइड स्कैफोल्ड का समावेश उच्च कार्यात्मक काइरल कोर तक पहुंचने की अनुमति देगा, जो कि मूल स्कैफोल्ड की तुलना में उच्चतर बायोएक्टिविटीज हो सकता है।

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Abbreviation	Full form
Å	Angstrom
AcOH	Acetic acid
AIBN	Azobisisobutyronitrile
Ar	Aryl
atm	Atmosphere
BDD	Boron-Doped Diamond
Bn	Benzyl
°C	Degrees Celsius
CAN	Ceric Ammonium Nitrate
$CDCl_3$	Deuterated chloroform
CH_2Cl_2	Dichloromethane
cm^{-1}	Wavenumbers
d	Doublet
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-Dichloroethane
dd	Doublet of doublets
DDQ	2.3-Dichloro-5,6-dicyanobenzoquinone
DFT	Density Functional Theory
DIPEA	*N*, *N*-Diisopropylethylamine
DMA	Dimethylacetamide
DMAP	*N*, *N*-Dimethylpyridin-4-amine
DME	1,2-Dimethoxyethane
DMF	Dimethylformamide
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
dr	Diastereomeric ratio
DTBP	Di-*tert*-butyl peroxide

ee	Enantiomeric excess
EPR	Electron Paramagnetic Resonance
equiv	Equivalent
er	Enantiomeric ratio
ESI	Electrospray ionization
Et_2O	Diethyl ether
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
FTIR	Fourier Transform Infrared
g	Lande Factor
GC-MS	Gas Chromatography-Mass Spectrometry
h	Hour
HFIP	1,1,1,3,3,3-Hexafluoroisopropanol
HMPA	Hexamethylphosphoramide
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
iPr_2S	Diisopropylsulfide
J	Coupling constant
m	Multiplet
m-CPBA	*meta*-Chloroperoxybenzoic acid
MCR	Multi-Component Reaction
MeOD	Deuterated methanol
MeOH	Metahnol
mg	Milligram
MHz	Megahertz
min	Minute
ml	Milliliter
MS	Mass Spectrometry
MS	Molecular Sieve
PAHs	Polycyclic Aromatic Hydrocarbons
PIFA	Bis(trifluoroacetoxy)iodo)benzene
PivOH	Pivalic acid

POPI	potassium phthalimide
r.t.	Room Temperature
s	Singlet
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBHP	*tert*-Butyl hydroperoxide
^{t}Bu	*tert*-Butyl
TFA	Trifluoroacetic acid
TfOH	Triflic acid
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TsCl	4-Toluenesulfonyl chloride
TTFA	Thalium Trifluoroacetate
UV- vis	Ultraviolet-visible
δ	Chemical shift
λ	Wavelength
μL	Microliter