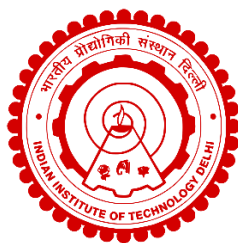


STEREOSELECTIVE 1,4- AND 1,6-ADDITION TO QUINONE METHIDES

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June 2023

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by

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Department of Chemistry

Submitted

In fulfillment of requirements of degree of the Doctor of Philosophy

to the



Indian Institute of Technology Delhi

June 2023

*Dedicated to my beloved Parents,
And
Family members.*

CERTIFICATE

This is to certify that the thesis entitled, “**Stereoselective 1,4- and 1,6-addition to Quinone Methides**”, being submitted by **Mr. Amjad Ali** to the *Indian Institute of Technology Delhi* for the award of the degree of **Doctor of Philosophy** in Chemistry is a record of bona fide research work carried out by him. **Mr. Amjad Ali** worked under my guidance and supervision and has fulfilled the requirements for the submission of a Ph.D. thesis, which to my knowledge has reached the requisite standard.

The results illustrated and incorporated 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.

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Amjad Ali

Abstract

This Ph.D. thesis entitled “**Stereoselective 1,4- and 1,6-addition to Quinone Methides**” deals with the development of protocols for the stereoselective reactions that are divided into five chapters. The first chapter is introduction briefly describes about chiral induction and homologation approaches. Next two chapters 2 and 3 of this dissertation deal with the enantioselective [4+2] annulation reaction and vinylogous 1,6-addition reactions respectively. Chapter 4 involves the umpolung process to generate α -phosphyloxy anion *via* [1,2]-phospha-Brook rearrangement and its subsequent addition to afford phosphate-bearing adducts. Chapter 5 is sub-divided into 5a, 5b, and 5c that involve a sequential transformation in one-pot, herein, the first step $P(NMe_2)_3$ mediates *in situ* generation of dispiro-cyclopropane adduct which in presence of Lewis acid undergoes homologation or intramolecular cyclization to furnish the corresponding products.

Chapter 1 briefly describes the Brook rearrangement and [1,2]-phospha-Brook rearrangements. The importance of chirality with various interesting examples of compounds having stereoisomers has been demonstrated. An introduction to asymmetric catalysis with an emphasis on organocatalysis has been elaborated. The homologation approaches are also described that involve the ring expansion.

Chapter 2 describes a chiral base-catalyzed cascade reaction involving *o*-quinone methides and *N*-Boc oxindoles is explored with excellent selectivities. Here, *o*-quinone methides react with *N*-Boc oxindole in presence of a chiral cinchona alkaloid-derived base that induces the chirality in the molecule and afforded substituted coumarins in good yield and selectivities.

Chapter 3 deals with the vinylogous 1,6-addition of 4-methyl-3-cyano coumarin to *p*-QMs. Here, an environmentally benign reaction condition has been achieved. The 1,6-adducts are obtained in excellent yields in milder conditions. Broad substrate scopes are shown. Also, an enantioselective version of this reaction is attempted.

In chapter 4 addition of α -ketoamide to *p*-quinone methide initiated by dialkylphosphite in presence of organic base 1,8-Diazabicyclo(5.4.0)undec-7-ene (DBU) is explored. The coupling of dialkylphosphite to α -ketoamide in presence of a base follows [1,2]-phospha-Brook rearrangement, generating corresponding α -phosphyloxy enolates that are subsequently seized by *p*-quinone methides (*p*-QMs). The two-step one-pot 1,6-conjugate addition provides

effective access to a series of isatin incorporated phosphate-bearing 1,6-adducts having two vicinal tertiary carbons with good yields and selectivities.

The chapter 5a describes Lewis acid-mediated one-carbon homologation approach involving 1,2-aryl migration of dispiro-cyclopropane intermediate aids in installing *para*-quinone methide embedded 2-quinolinone cores with high yields and regioselectivity. Also, the synthetic modifications of obtained adduct were further derivatized by C-P, C-S, and C-C bond formation. Further, cyclopropanation of 2-quinolinone embedded *p*-QMs is also demonstrated affording a contiguous quarternary spiro centre.

In chapter 5b a diastereoselective protocol for synthesis of oxindole-containing spiro-substituted phenanthrenes has been established. The dispiro-cyclopropane intermediates were generated by the coupling of isatins and 2-aryl *p*-QMs *via* [1,2]-phospha-Brook rearrangement. Subsequently, the ring opening of cyclopropane in presence of Lewis acids leads to the formation of an *ortho*-aza-xylylene intermediate that undergoes intramolecular nucleophilic attack affording desired spiro adducts in good yield and diastereoselectivities.

The chapter 5c describes an efficient protocol for synthesis of 2,3-disubstituted phenalenone frameworks has been demonstrated through one-pot procedure. Here, the sequential addition of P(NMe₂)₃ and Lewis acid lead the installation of phenalenone core. Firstly, P(NMe₂)₃ mediates the *in situ* generation of dispiro-cyclopropane ring by the coupling of acenaphthoquinone to *p*-QMs *via* [1,2]-phospha-Brook rearrangement followed by intramolecular cyclization, then Lewis acid mediate the homologation of dispiro-cyclopropane adduct to 2,3-disubstituted phenalenones. This methodology demonstrates the use of unconventional 1,2-carbonyl migration in the ring expansion affording substituted phenalenones with very broad substrate scope.

यह पीएच.डी. थीसिस जिसका शीर्षक “त्रिविम चयनात्मक 1,4- and 1,6-क्विनोन मेथाइड्स से जोड़” पांच अध्यायों में विभाजित त्रिविम प्रतिक्रियाओं के लिए प्रोटोकॉल के विकास से संबंधित है। इस शोध प्रबंध के पहले दो अध्याय एनेंटियोसेलेक्टिव [4+2] विलोपन अभिक्रिया और विनालॉगस 1,6-योगात्मक अभिक्रिया से संबंधित हैं। अध्याय 4 में [1,2]-फॉस्फा-ब्रुक पुनर्व्यवस्था के माध्यम से अनपोलंग प्रक्रिया शामिल है जो फॉस्फेट-असर व्यसनों को उत्पन्न करती है। अध्याय 5 को उप-अध्यायों 5a, 5b और 5c में विभाजित किया गया है। अध्याय 5ए, 5बी, और 5सी में क्रमिक रूप से रूपांतरित एक-पॉट दो-चरणीय प्रक्रिया शामिल है, यहां, पहले चरण में $P(NMe_2)_3$ डिस्पिरो-साइक्लोप्रोपेन जोड़ की सीटू पीढ़ी में मध्यस्थता करता है जो लुईस एसिड की उपस्थिति में होमोलोगेशन या इंट्रामोलेक्युलर साइक्लाइज़ेशन से गुजरता है संबंधित उत्पादों को प्रस्तुत करने के लिए।

अध्याय 1: ब्रुक पुनर्विनयास और [1,2] फोसा-ब्रुक पुनर्विनयास का संक्षिप्त विवरण। विभिन्न रोचक उदाहरणों के साथ त्रिविम रसायन के महत्व को प्रदर्शित किया गया है। ऑर्गोकेटलिसिस पर जोर देने के साथ असममित कटैलिसिस का परिचय वर्णित किया गया है। होमोलोगेशन दृष्टिकोण का भी वर्णन किया गया है जिसमें रिंग का विस्तार शामिल है।

अध्याय 2: ओ-क्विनोन मेथाइड्स और एन-बोक ऑक्सिंडोल्स को शामिल करने वाली एक काइरल बेस-उत्प्रेरित कैस्केड अभिक्रिया को उत्कृष्ट चयनात्मकताओं के साथ खोजा गया है। यहाँ, ओ-क्विनोन मेथाइड्स एक काइरल सिनकोना अल्कलॉइड-व्युत्पन्न आधार की उपस्थिति में एन-बोक ऑक्सिंडोल के साथ अभिक्रिया करता है जो अणु में काइरलता को प्रेरित करता है और अच्छी उपज और चयनात्मकताओं में प्रतिस्थापित क्यूमेरिन को वहन करता है।

अध्याय 3: पी-क्यूएम में 4-मिथाइल-3-साइनो कौमारिन का विनालॉगस 1,6-जोड़ पर्यावरण की दृष्टि से सौम्य अभिक्रिया स्थिति के साथ हासिल किया गया है। 1,6-व्यसनों को दुधारू परिस्थितियों में उत्कृष्ट पैदावार प्राप्त होती है। ब्रॉड सबस्ट्रेट स्कोप दिखाए जाते हैं। इसके अलावा, इस अभिक्रिया का एक ऊर्जावान संस्करण का प्रयास किया गया है।

अध्याय 4: कार्बनिक आधार 1,8-डायजाबिसाइक्लो (5.4.0) अनडेक-7-ईन (डीबीयू) की उपस्थिति में डाईएलकिल फॉस्फेट द्वारा शुरू किए गए पी-क्विनोन मेथाइड के लिए α -केटोएमाइड के अतिरिक्त का पता लगाया गया है। एक आधार की उपस्थिति में α -केटोमाइड के लिए डाईएलकिल फॉस्फेट का युग्मन [1,2]-फॉस्फा-ब्रुक पुनर्विनयास का अनुसरण करता है, जिससे संबंधित α -फॉस्फोनीलॉक्सी एनोलेट्स

उत्पन्न होते हैं जो बाद में पी-क्विनोन मेथाइड्स (पी-क्यूएम) द्वारा जब्ज किए जाते हैं। टू-स्टेप वन-पॉट 1,6-कंजुगेट एडिशन आइसैटिन की एक श्रृंखला के लिए प्रभावी पहुंच प्रदान करता है जिसमें अच्छी पैदावार और चयनात्मकता के साथ दो वाइसिनल तृतीयक कार्बन वाले फॉस्फेट-सहित 1,6-एडक्ट्स शामिल हैं। अध्याय 5ए: लुईस एसिड-मध्यस्थता वाला एक-कार्बन होमोलोगेशन दृष्टिकोण जिसमें डिस्पिरो-साइक्लोप्रोपेन इंटरमीडिएट के 1,2-एरिल माइग्रेशन शामिल है, जो उच्च पैदावार और प्रतिगामीता के साथ पैरा-क्विनोन मेथाइड एम्बेडेड 2-क्विनोलिनोन कोर स्थापित करने में सहायता करता है। इसके अलावा, प्राप्त जोड़ के सिंथेटिक संशोधनों को सी-पी, सी-एस और सी-सी बांड गठन द्वारा आगे व्युत्पन्न किया गया था। इसके अलावा, 2-क्विनोलिनोन एम्बेडेड पी-क्यूएम के साइक्लोप्रोपेनेशन को भी एक सन्निहित त्रैमासिक स्पाइरो केंद्र के रूप में प्रदर्शित किया जाता है।

अध्याय 5बी: ऑक्सीडोल-युक्त स्पाइरो-प्रतिस्थापित फेनेथ्रीन के संश्लेषण के लिए एक डायस्टेरोसेलेक्टिव प्रोटोकॉल स्थापित किया गया है। [1,2]-फॉस्फा-ब्रूक पुनर्विनयास के माध्यम से आइसोतिन और 2-एरिल पी-क्यूएम के युग्मन द्वारा डिस्पिरो-साइक्लोप्रोपेन मध्यवर्ती उत्पन्न किए गए थे। इसके बाद, लुईस एसिड की उपस्थिति में साइक्लोप्रोपेन के रिंग के खुलने से एक ऑर्थो-एज़ा-ज़ाइलिलीन इंटरमीडिएट का निर्माण होता है जो इंटरमोल्युलर न्यूक्लियोफिलिक आक्रमण से गुजरता है जो अच्छी उतपाद और डायस्टेरोसेलेक्टिविटी में वांछित स्पाइरो व्यसनों की पुष्टि करता है।

अध्याय 5सी: 2,3-डिस्बिस्टिट्यूटेड फेनालेनोन फ्रेमवर्क के संश्लेषण के लिए एक कुशल प्रोटोकॉल को एक-पॉट प्रक्रिया के माध्यम से प्रदर्शित किया गया है। यहां, $P(NMe_2)_3$ और लुईस एसिड के अनुक्रमिक जोड़ से फेनालेनोन कोर की स्थापना होती है। सबसे पहले, $P(NMe_2)_3$ [1,2]-फॉस्फा-ब्रूक पुनर्विनयास के माध्यम से [1,2]-फॉस्फा-ब्रूक पुनर्विनयास के माध्यम से एसेनाफथोक्विनोन के युग्मन द्वारा डिस्पिरो-साइक्लोप्रोपेन रिंग की सीटू पीढ़ी में मध्यस्थता करता है, फिर लुईस एसिड डिस्पिरो के होमोलॉगेशन की मध्यस्थता करता है। -साइक्लोप्रोपेन अपडक्ट टू 2,3-डिस्बिस्टिट्यूटेड फेनालेनोन। यह कार्यप्रणाली रिंग विस्तार में अपरंपरागत 1,2-कार्बोनिल माइग्रेशन के उपयोग को प्रदर्शित करती है, जो बहुत व्यापक सबस्ट्रेट दायरे के साथ फेनालेनोन को प्रतिस्थापित करती है।

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List of Abbreviations

Abbreviation	Full form
Ac	Acetate
MeCN/CH ₃ CN/ACN	Acetonitrile
Ar	Aryl
BF ₃ .OEt ₂	Boron trifluoride etherate
Bn	Benzyl
Boc	<i>tert</i> -butyloxycarbonyl
^t Bu	<i>tert</i> -Butyl
CDCl ₃	Deuterated chloroform
CH ₂ Cl ₂	Dichloromethane
CPME	Cyclopentyl methyl ether
cm ⁻¹	Wavenumbers
°C	Degrees Celsius
2,4-DNBA	2,4-Dinitrobenzoic acid
<i>dr</i>	Diastereomeric ratio
DIPEA	<i>N, N</i> -Diisopropylethylamine
DMAP	<i>N, N</i> -Dimethylpyridin-4-amine
DEPT	Distortionless enhancement by polarization transfer
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
d	Doublet
dd	Doublet of doublets
DMSO-d ₆	Deuterated dimethyl sulfoxide
δ	Chemical shift
<i>er</i>	Enantiomeric ratio
<i>ee</i>	Enantiomeric excess
ESI-TOF	Electrospray ionization - Time-of-flight
EtOAc	Ethyl acetate
FTIR	Fourier transform infrared
H ₂ O	Water
h	Hour
HCN	Hydrogen cyanide
HOMO	Highest occupied molecular orbital
HPLC	High-performance liquid chromatography
<i>J</i>	Coupling constant
λ	Wavelength
LUMO	Lowest unoccupied molecular orbital
min	Minute

MTBE	Methyl <i>tert</i> -butyl ether
m	Multiplet
MHz	Megahertz
mL	Millilitre
MeOD	Deuterated methanol
μ L	Microlitre
PNBA	<i>para</i> -Nitrobenzoic acid
<i>p</i> -TsOH	<i>para</i> -Toluenesulfonic acid
PMA	Phosphomolybdic acid
s	Singlet
SOMO	Singly unoccupied molecular orbital
TFA	Trifluoroacetic acid
TfOH	Triflic acid
TCA	Trichloroacetic acid
THF	Tetrahydrofuran
TMS	Tetramethylsilane
TBAF	Tetra- <i>N</i> -butylammonium fluoride
UV	Ultraviolet