OXIDATIVE FUNCTIONALIZATION AND HETEROCYCLIZATION MEDIATED BY DIB, PhIO AND SELECTFLUOR™

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OXIDATIVE FUNCTIONALIZATION AND HETEROCYCLIZATION MEDIATED BY DIB, PhIO AND SELECTFLUOR™

by

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Submitted
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CERTIFICATE

This is to certify that the thesis entitled, **"*OXIDATIVE FUNCTIONALIZATION AND HETEROCYCLIZATION MEDIATED BY DIB, PHIO AND SELECTFLUOR^{TM}.*"** being submitted by **Ms. Alankrita Garia** to the Indian Institute of Technology, Delhi for the award of the degree of **Doctor of Philosophy** in Chemistry, is a record of bonafide research work carried out by her. **Ms. Alankrita Garia** has 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 award of any degree or diploma.

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ABSTRACT

Chapter 1 provides general overview of polyvalent organoiodine compounds in terms of their historical background, classification, nomenclature, structural features, hypervalent bonding and principles of reactivity. This chapter mainly focuses on the synthetic aspects of DIB, PhIO especially in the synthesis of the heterocyclic molecules. It also briefly describes about synthetic utility of selectfluor™ in organic synthesis.

In **Chapter 2** an unprecedented synthesis of fused quinazolinones from N-pyridylindoles under oxidative conditions using a combination of (diacetoxyiodo)benzene and $K_2S_2O_8$ is reported. The reaction is metal-free, has a broad substrate scope, is operationally simple with short reaction time, and provides 11*H*-pyrido[2,1-*b*]quinazolin-11-one derivatives in moderate to high yields. It is believed to proceed via an in situ generated 2-hydroxy-1-(pyridin-2-yl)indolin-3-one as the key reaction intermediate, which undergoes a C–C bond cleavage to produce an electrophilic C-3 site in *N*-pyridyl indole. Subsequent nucleophilic attack by pyridyl nitrogen results in its cyclization.

In **Chapter 3** a unique lactonization of 2-methyl-3-acyl-4-phenylquinolines using PhIO as the oxidant and selectfluor™ as an additive is reported. The reaction occurs under ambient conditions through tandem oxidation and cyclization of sp^3 C–H bonds under metal-free conditions. The heterocycle-fused lactones are obtained in moderate to good yield.

In **Chapter 4** Metal-free synthesis of anthranils from *ortho*-carbonyl anilines using PhIO as a sole reagent under ambient conditions demonstrated. This methodology did not require any external additives and delivered anthranils in excellent yields with broad substrate scope. The mechanistic studies suggest that the reaction proceeds via *in-situ* generation of iminoiodane leading to nitrene and a subsequent nucleophilic attack from oxygen of *ortho*-carbonyl aniline on nitrene results in heterocyclization.

In **Chapter 5** an unprecedented tandem *ortho*-selective fluorination and 1,3-carbonyl migration in *ortho*-carbonyl anilines using selectfluor™ as the sole reagent is reported. The reaction is transition-metal free, does not require any pre-functionalization, takes place under ambient conditions, and yields *ortho*-fluoroanilide derivatives in moderate to good yields. Selectfluor™

serves the dual purpose of fluorine source and assists 1,3-carbonyl migration. The formation of proposed charge transfer (CT) complex between *ortho*-carbonyl aniline (donor) and selectfluor^{TM} (acceptor), and its role in enabling the observed *ortho*-selectivity is supported by experimental and computational investigations. The single-electron-transfer (SET) in the complex results in the formation of (2-amino-3-fluorophenyl)(phenyl)methanone intermediate, which on subsequent 1,3-carbonyl migration forms *ortho*-fluoroanilide in presence of F^+ or *in-situ* generated H^+.

सार

अध्याय 1 हाइपरवैलेंट ऑर्गेनोडीन के ऐतिहासिक पृष्ठभूमि, वर्गीकरण, नामकरण, संरचनात्मक विशेषताओं, हाइपरवैलेंट बॉन्डिंग और प्रतिक्रियाशीलता के सिद्धांतों के संदर्भ में सामान्य अवलोकन प्रदान करता है। यह अध्याय मुख्य रूप से डीआईबी, पीएचआईओ के सिंथेटिक पहलुओं पर विशेष रूप से हेट्रोसायक्लिक अणुओं के संश्लेषण पर केंद्रित है। यह कार्बनिक संश्लेषण में सेलेक्टफ्लोरटीएम की सिंथेटिक उपयोगिता के बारे में भी संक्षेप में बताता है।

अध्याय 2 में (डायसेटोक्सीआयोडो) बेंजीन और $K_2S_2O_8$ के संयोजन का उपयोग करके ऑक्सीडेटिव स्थितियों के तहत एन-पाइरीडिलिंडोल्स से जुड़े हुए क्विनाज़ोलिनोन के अभूतपूर्व संश्लेषण की सूचना दी गई है। प्रतिक्रिया धातु मुक्त है, एक व्यापक सब्सट्रेट गुंजाइश है, कम प्रतिक्रिया समय के साथ परिचालन रूप से सरल है, और मध्यम से उच्च पैदावार में 11 एच-पाइरिडो [2,1-बी] क्विनाज़ोलिन-11-एक डेरिवेटिव प्रदान करता है। ऐसा माना जाता है कि यह एक प्रमुख प्रतिक्रिया मध्यवर्ती के रूप में उत्पन्न 2-हाइड्रॉक्सी-1-(पाइरिडिन-2-वाईएल) इंडोलिन-3-एक के माध्यम से आगे बढ़ता है, जो एक इलेक्ट्रोफिलिक सी -3 साइट का उत्पादन करने के लिए सी-सी बंधन दरार से गुजरता है। एन-पाइरिडाइल इंडोल में। पाइरिडाइल नाइट्रोजन के बाद के न्यूक्लियोफिलिक हमले के परिणामस्वरूप इसका चक्रण होता है।

अध्याय 3 में 2-मिथाइल-3-एसिल-4-फेनिलक्विनोलिन के एक अद्वितीय लैक्टोनाइजेशन के बारे में बताया गया है जिसमें , पीएचआईओ को ऑक्सीडेंट के रूप में और सेलेक्टफ्लोरटीएम को एडिटिव के रूप में उपयोग किया जाता है। प्रतिक्रिया परिवेशी परिस्थितियों में अग्रानुक्रम ऑक्सीकरण और धातु-मुक्त परिस्थितियों में sp^3 C-H बांडों के चक्रीकरण के माध्यम से होती है। हेटरोसायकल-फ्यूज्ड लैक्टोन मध्यम से अच्छी उपज में प्राप्त होते हैं।

अध्याय 4 में परिवेशी परिस्थितियों में एकमात्र अभिकर्मक के रूप में पीएचआईओ का उपयोग करते हुए ऑर्थो-कार्बोनिल एनिलिन से एंथ्रानिल के धातु-मुक्त संश्लेषण का प्रदर्शन किया गया। इस पद्धति में किसी बाहरी योजक की आवश्यकता नहीं थी और व्यापक सब्सट्रेट गुंजाइश के साथ उत्कृष्ट पैदावार में एंथ्रैनिल वितरित किए गए थे। यंत्रवत अध्ययनों से पता चलता है कि यह प्रतिक्रिया इमिनोइओडेन की इन-सीटू पीढ़ी के माध्यम से नाइट्रीन की ओर ले जाती है और नाइट्रीन पर ऑर्थो-कार्बोनिल एनिलिन के ऑक्सीजन से न्यूक्लियोफिलिक हमले के परिणामस्वरूप हेटरोसाइक्लाइज़ेशन होता है।

अध्याय 5 में एकमात्र अभिकर्मक के रूप में सेलेक्टफ्लोरटीएम का उपयोग करते हुए ऑर्थो-कार्बोनिल एनिलिन में एक अभूतपूर्व अग्रानुक्रम ऑर्थो-चयनात्मक फ्लोरिनेशन और 1,3-कार्बोनिल प्रवासन की सूचना दी गई है। प्रतिक्रिया संक्रमण-धातु मुक्त है, किसी भी पूर्व-कार्यात्मकता की आवश्यकता नहीं है, परिवेश की परिस्थितियों में होती है, और मध्यम से अच्छी पैदावार में ऑर्थो-फ्लोरोएनिलाइड डेरिवेटिव उत्पन्न करती है। सेलेक्टफ्लोरटीएम फ्लोरीन स्रोत के दोहरे उद्देश्य को पूरा करता है और 1,3-कार्बोनिल प्रवासन में सहायता करता है। ऑर्थो-कार्बोनिल एनिलिन (दाता) और सेलेक्टफ्लोरटीएम (स्वीकर्ता) के बीच प्रस्तावित चार्ज ट्रांसफर (सीटी) कॉम्प्लेक्स का गठन, और प्रेक्षित ऑर्थो-चयनात्मकता को सक्षम करने में इसकी भूमिका प्रयोगात्मक और कम्प्यूटेशनल जांच द्वारा समर्थित है। सिंगल-इलेक्ट्रॉन-ट्रांसफर जटिल परिणाम में (2-एमिनो-3-फ्लोरोफिनाइल) (फिनाइल) मीथेनोन इंटरमीडिएट के गठन में होता है, जो बाद में 1,3-कार्बोनिल माइग्रेशन पर एफ + या एच+। की उपस्थिति में ऑर्थो-फ्लोरोएनिलाइड बनाता है। एच+। इन-सीटू उत्पन्न होता है।

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GLOSSARY OF SYMBOLS AND ABBREVIATIONS

Ac	Acetyl
ACN	Acetonitrile
Ag	Silver
AgF	Silver (I) fluoride
AgF_2	Silver (II) fluoride
$AgNO_3$	Silver (I) nitrate
AgOTf	Silver trifluoromethanesulfonate
$Al(NO_3)_3$	Aluminium nitrate
anh. $(CH_3)_4NF$	Anhydrous tetramethyl ammonium fluoride
APTs	Aza-podophyllotoxins
$ArB(OH)_2$	Aryl boronic acid
$ArI(CN)_2$	Dicyanoiodoarenes
$ArIO_2$	Iodylarene
Ar_2IX	Diaryliodonium salt
AZADO	2-Azaadamantane-*N*-oxyl
BaO	Barium oxide
BDE	Bond dissociation energy
$BF_3.Et_2O$	Borontrifluoride etherate
BOC	*tert*-butyloxycarbonyl
BQ	1,4-Benzoquinone
Bu_4NI	Tetra-butyl ammonium iodide
$BUPAd_2$	Di(1-adamantyl)-n-butylphosphine hydriodide
Calcd.	Calculated
$CDCl_3$	Deuterated chloroform
CF_3OF	Trifluoromethyl hypofluorite
CO	Carbon monoxide
$CsCO_3$	Cesium carbonate
CsF_2	Cesium fluoride
Cu	Copper
$-CH_3$	Methyl group
CuBr	Copper(I) bromide
$Cu(OTf)_2$	Copper triflate
$Cu(OTf)_2 \cdot$Toluene	Copper triflate·Toluene complex
CuI	Copper iodide

CuO	Copper oxide
CuTC	Copper(I) thiophene-2-carboxylate
COX	Cyclooxygenase
DAST	Diethylaminosulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*, *N*′-Dicyclohexylcarbodiimide
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DFI	2,2-Difluoro-1,3-dimethylimidazolidine
DIB	(Diacetoxyiodo)benzene or PIDA (Phenyliodinediacetate) or $PhI(OAc)_2$
DIBPP	1,3-bis(diisobutylphosphino)propane
DMA	Dimethylacetamide
DMF	Dimethylformamide
DMPU/HF	Tetrahydro-1,3-dimethyl-2(1*H*)-pyrimidinone Hydrofluoride
DMDO	Dimethyldioxirane
DMSO	Dimethyl sulfoxide
DPIB	Dipivaloyloxyiodobenzene
E^+	Electrophile
EDCI	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI-MS	Electron spray ionization mass spectrometry
Equiv	Equivalent
Et_3NH	Ethanol
EtOAc	Ethyl acetate
EtOH	Ethanol
EWG	Electron-withdrawing group
EXAFS	Extended X-Ray Absorption Fine Structure
GC-MS	Gas chromatography–mass spectrometry
h	Hour
HBF_4	Tetrafluoroboric acid
HBpin	Pinacolborane
HCOOH	Formic acid
Het	Hetero
aq. HF	Hydrofluoric acid
HFIP	Hexafluoro-2-propanol
$HF{:}NH_3$	Triethylamine trihydrofluoride
HgO	Mercuric oxide
HIO_4	Periodic acid
HIV-1	Human immunodeficiency virus
HRMS	High resolution mass spectroscopy

Hz	Hertz
IBD	Iodobenzene diacetate
IBDA	Iodosobenzene diacetate
IBX	2-Iodoxybenzoic acid
IF_7	Iodine heptafluoride
I_2	Iodine
KBr	Potassium bromide
K_2CO_3	Potassium carbonate
KF	Potassium fluoride
$KHCO_3$	Potassium bicarbonate
$KHSO_5$	Potassium peroxymonosulfate
KI	Potassium iodide
KO^tBu	Potassium tert-butoxide
$K_2S_2O_8$	Potassium peroxydisulfate
LED	Light Emitting Diode
LSF	Late-stage functionalization
MeOH	Methanol
Mg	Milligram
$MgSO_4$	Magnesium sulphate
MHz	Megahertz
Min.	Minutes
mL	Mililitre
MOT	Molecular orbital theory
MS	Molecular sieves
MW	Microwave
m/z	Mass by charge ratio
N_2	Under nitrogen atmosphere
NaBr	Sodium bromide
$NaBF_4$	Sodium tetrafluoroborate
NaH	Sodium hydride
$NaHPO_4$	Sodium hydrogen phosphate
NaOAc	Sodium acetate
NaOH	Sodium hydroxide
NBS	N-Bromosuccinimide
nBu_4NF	Tetra-n-butylammonium fluoride
NFASs	*N*-fluoro-*N*-arylsulfonamides
NFPy	*N*-fluoropyridinum salts
NFSI	*N*-Fluorobenzenesulfonimide
$(NH_4)_2S_2O_8$	Ammonium persulfate

$NH_2OH{\cdot}HCl$	Hydroxylamine hydrochloride
NMR	Nuclear magnetic resonance
NaN_3	Sodium azide
Na_2SO_4	Sodium sulphate
Nu	Nucleophile
-OAc	Acetoxy
-OBn	Benzoyl
$-OCH_3$	Methoxy group
ORTEP	Oak Ridge Thermal Ellipsoid Plot
-OTf	Trifluoromethanesulphonate
Pd	Palladium
PDAIS	Poly[4-diacetoxyiodo]styrene
$Pd(OAc)_2$	Palladium acetate
PET	Positron emission tomography
Ph	Phenyl
PhI	Phenyl iodide
Ph_3I	Triphenyl iodine
$PhICl_2$	(dichloroiodo)benzene
$PhIF_2$	(difluoroiodo)benzene
PIFA	Phenyliodine bis(trifluoroacetate)
$PhI(N_3)_2$	Diazido(phenyl)-λ^3-iodane or azidoiodane
PhINTs	(Tosylimino)phenyl- λ^3-iodane or Tosyliminoiodane
$PhI(NTs_2)_2$	*N*,*N*-(phenyl-λ^3-iodanediyl)bis(4-methyl-*N*-tosylbenzenesulfonamide)
PhIO	Iodosylbenzene or iodosobenzene
$Ph_2IO(OAc)$	Diphenyliodyl acetate
$PhI(OAc)NTs_2$	((4-methyl-*N*-tosylphenyl)sulfonamido)(phenyl)-λ^3-iodanyl acetate
$PhIO{\cdot}BF_3$	Iodosylbenzene–Boron trifluoride etherate
$PhI(OH)BF_4{\cdot}18C_6$	Hydroxy(phenyl)(tetrafluoroborato)-λ3-iodane·18-Crown-6 Complex
$PhI(OH)O_3SAr$	Hydroxy(phenyl)-λ^3-iodanyl arylsulfonate
$(PhIO)_3{\cdot}SO_3$	Iodosylbenzene sulfate
PhMe	Toluene
p-$TolIF_2$	*p*-(Difluoroiodo)toluene
Py	Pyridine
Rf	Retention Factor
Rt	Room Temperature

$Ru(bpy)_3PF_6$	Ruthenium-tris(2,2′-bipyridyl) dihexafluorophosphate
SDS	Sodium dodecyl sulfate
Selectfluor™	1-Chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
SET	Single electron transfer
SPECT	Single-photon emission computed tomography
t-Bu	tert-butyl group
TBHP	tert-Butyl hydroperoxide
TCB/TCNB	1,2,4,5-Tetracyanobenzene
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl) oxidanyl
Temp.	Temperature
TFA	Trifluoroacetic acid
TFE	Tetrafluoroethylene
Tf	Trifluoromethanesulfonate or triflate
Tf_2NH	Trifluoromethanesulfonimide
TfOH	Trifluoromethanesulfonic acid
THF	Tetrahydrofuran
$TiCl_4$	Titanium tetrachloride
$TiBr_4$	Titanium tetrabromide
TIPBSA	2,4,5-Tris-isopropylbenzene sulfonic acid
TLC	Thin Layer Chromatography
TMSOTf	Trimethylsilyl trifluoromethanesulfonate
TMS	Tetramethylsilane
TMSCN	Trimethylsilyl cyanide
TOF	Time of Flight
Ts	*para*-Tolunesulfonyl
UV	Ultra-violet
XeF_2	Xenon difluoride
$Zn(ClO_4)_2 \cdot H_2O$	Zinc perchlorate hexahydrate

MATERIALS AND METHODS

Physical measurements

NMR spectra (^{1}H and ^{13}C) were measured on a Bruker DPX-300/400/500 MHz spectrometer. HRMS were recorded on MICROTOF-Q ll 228888.10262 using electrospray ionization (ESI) as the ionization method. Reaction optimization were done on GC-MS (Perkin Elmer Clarus 600 C). IR spectra were recorded on Nicolet 460 (Protege) spectrophotometer in range 4000-400 cm-1. UV-vis spectroscopy was recorded on SHIMADZU-UV-2450 spectrophotometer.

Single-crystal X-ray data of compounds was collected on Bruker SMART CCD-Diffractometer using graphite monochromated Mo*K*α radiation (λ = 0.71073 Å). The data integration and reduction were processed with Crys Alis Pro software. The structures were solved by the direct method and then refined on *F*2 by the full matrix least-squares technique with the SHELX-97 set of software using the WinGX (version 1.80.05) program package. All non-hydrogen atoms were refined anisotropically and hydrogen atoms were treated as riding atoms using SHELX default parameters. Molecular structures have been drawn using Diamond software. Copies of the data can be found free of charge upon application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033. e-mail: deposit@ccdc.cam.ac.uk.

Analytical Information

All the isolated compounds were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS using $CDCl_3$, D_2O, CD_3OD and DMSO as the solvents with tetramethylsilane (TMS) as the internal standard at room temperature. Chemical shifts are given in δ (ppm) relative to TMS, the coupling constants (*J)* are given in hertz (Hz).

Chemicals and reagents

All reactions were carried out under N_2/air atmosphere in oven dried round bottom flask/18 ml reaction tube with/without septum cover. All the solvents were bought from Aldrich, Alfa-aesar, Merck, Thermo Fisher and Spectrochem were used. For column chromatography, silica gel (230–400 mesh) from SRL Co. was used. A gradient elution using ethyl acetate-hexane was performed on Merck aluminium TLC sheets (silica gel 60F254).