COPPER CATALYZED SYNTHESIS OF BIOLOGICALLY RELEVANT HETEROCYCLES

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COPPER CATALYZED SYNTHESIS OF BIOLOGICALLY RELEVANT HETEROCYCLES

by

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I affectionately dedicate this thesis to my loving daughter "Pranya", and husband "Pranjal" who is a guiding lamp and source of inspiration always.

CERTIFICATE

This is to certify that the thesis entitled, **"COPPER CATALYZED SYNTHESIS OF BIOLOGICALLY RELEVANT HETEROCYCLES"** being submitted by **Mrs. Ananya Srivastava** 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. Mrs. Ananya Srivastava has worked under my guidance and supervision. She has fulfilled the requirements for the submission of this thesis, which to my knowledge has reached the requisite standard.

The results contained in this thesis have not been submitted, in part or in full, to any other university or institute for award of any degree or diploma.

Date:

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ABSTRACT

Chapter 1: An overview of the importance of heterocycles and their copper catalyzed synthesis *via* cross-coupling, C-H functionalization and cross dehydrogenative coupling reactions has been provided. Heterogeneous catalysts stabilized by ionic liquid and graphene have been discussed.

Chapter 2: To develop a mild, efficient and reusable system for copper catalyzed reactions, ethylacetoacetate has been doped into IL by tagging it with imidazolium cation stabilized by a counter hydroxide or acetate anion. The novel ligand-anchored ILs show high efficiency in generation and stabilization of uniformly dispersed Cu(I)I NPs with particle size in range 9-12 nm. Further, the catalytic system provides an efficient route to amination of aryl iodides, bromides and the less reactive chlorides under mild conditions with very low catalyst loading of only 2 mol % to yield primary aryl amines selectively. Furthermore, the reaction allows easy isolation of products with recovery of IL containing an intact built-in ligand and base combination for further reuse.

Chapter 3: A novel, regioselective, multicomponent, one-pot approach for the construction of benzoxazole-linked triazoles is discussed. The synthesis has been achieved in two sequential steps involving copper-catalyzed alkynylation of benzoxazole followed by a 1,3-dipolar cycloaddition reaction. Tests against clinical isolates of *Staphylococcus aureus* and *Escherichia coli* show potent Gram-negative activity for compounds **22a**, **22d**, and **22e**. The cytotoxicity of the synthesized library is determined against three cancer cell lines: HeLa, SKBr3, and Hep G2. Compound **22m** shows significant cytotoxicity against all the cell lines**.**

Chapter 4: A highly efficient copper-catalyzed intermolecular hydroindolation reaction of unactivated terminal alkynes to expeditiously synthesize bis(indolyl)alkanes in moderate to high yields is described. The double nucleophilic addition of two molecules of indole to one molecule of alkyne occurs in a tandem manner through an *anti*-Markovnikov pathway.

Various arenes and alkynes including phenyl acetylenes and trimethylsilylacetylene, allow for this transformation. Preliminary mechanistic study sheds light on the observed *anti*-Markovnikov addition involving a Cu-vinylidene complex, and 3-styryl-1H-indole as prominent intermediates.

Chapter 5: A GO-Cu(I)Br nanocatalyst has been prepared, and applied for the synthesis of bis(indolyl)methanes. The catalyst is highly effective, required in much lower amount (0.05 mol%), and is recyclable up to six reaction cycles without loss in activity. The synthesized compounds have been screened for their *in vitro* anti-HIV activity, and compound **25d** shows significant anti-HIV-1 effect. Molecular modelling of **25d** with reverse transcriptase enzyme has been carried out to understand its binding mechanism to the active enzyme site.

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GLOSSARY OF SYMBOLS AND ABBREVIATIONS

Å	:	Angstrom
a.u	:	Arbitrary unit
Ac	:	Acetic
AIDS	:	Acquired immunodeficiency syndrome
Approx.	:	Approximately
Ar	:	Aryl
BIM	:	Bis(indolyl)methane
$BMI.BF_4$	:	1-*n*-butyl-3-methylimidazolium tetrafluoroborate
$BMI.PF_6$	:	1-*n*-butyl-3-methylimidazolium hexafluorophosphate
BQ	:	Benzoquinone
^{13}C	:	13 Carbon
Cat	:	Catalyst
cps	:	Counts per second
DABCO	:	Diazabicyclooctane
DIB	:	Diacetoxyiodobenzene
DCE	:	Dichloromethane
DLS	:	Dynamic light scattering
DMF	:	Dimethylformamide
DMSO	:	Dimethyl sulfoxide
EAA	:	Ethylacetoacetate
EDX	:	Energy-dispersive X-ray spectroscopy
Equiv	:	Equivalent
Et	:	Ethyl
eV	:	Electron volt
^{19}F	:	19 Fluorine

Fcc	:	Face centered cubic
FTIR	:	Fourier transform infrared spectroscopy
g	:	Gram
G	:	Graphene
GO	:	Graphene oxide
^{1}H	:	Proton
h	:	Hour
HIV	:	Human immunodeficiency virus
HPLC	:	High performance liquid chromatography
Hz	:	Hertz
IC_{50}	:	Inhibitory concentration 50%
IL	:	Ionic liquid
i-Pr	:	*iso*-propyl
JCPDS	:	Joint Committee on Powder Diffraction Standards
kV	:	Kilovolt
L	:	Litre
M	:	Molar
mg	:	Milligram
MIC	:	Minimum inhibitory concentration
min	:	Minute
mL	:	Millilitre
mmol	:	Millimol
MW	:	Microwave
NBS	:	*N*-bromosuccinimide
n-Bu	:	Butyl
nm	:	Nanometre

NMP	:	N-methyl pyrolidinone
NMR	:	Nuclear magnetic resonance
%	:	Percent
Ppm	:	Parts per million
PTSA	:	*para*-toluenesulfonic acid
PXRD	:	Powder X-ray diffraction
RO	:	Reduced graphene oxide
Rpm	:	Rotation per minute
r.t.	:	Room temperature
S.No	:	Serial number
SEM	:	Scanning electron microscope
TBHP	:	*tert*-butyl hydroperoxide
t-Bu	:	Tertiary butyl
TEM	:	Transmission electron microscope
Temp	:	Temperature
TEMPO	:	2,2,6,6-Tetramethyl-1-piperidinyloxy
Tert	:	Tertiary
THF	:	Tetrahydrofuran
TLC	:	Thin layer chromatography
UV	:	Ultra-Violet
Vis	:	Visible
XPS	:	X-ray Photoelectron Spectroscopy
α	:	Alpha
β	:	Beta
µL	:	Microlitre
ϒ	:	Gamma

MATERIALS AND METHODS

Physical measurement:

NMR spectra (^{1}H and ^{13}C) were measured on a Bruker DPX-300 MHz spectrometer (^{1}H 300 & 400 MHz, ^{13}C 75MHz). HRMS were recorded on MICROTOF-Q ll 228888.10262 using electrospray ionization (ESI) as the ionization method. The size of nanoparticles was determined by Malvern DLS nano ZS90. EDX spectra were recorded on ZEISS EVO 50 model QuanTax 200 which is based on the SDD technology and provides an energy resolution of 127 eV at Mn K alpha.

Powder X-ray diffraction (PXRD) data was collected on X-ray diffractometer (Bruker). Raman spectroscopy was performed using the 2.54 eV (488 nm) line of an Ar ion laser on a HORIBA JOBIN YVON Lab RAM HR 800 instrument by placing a pellet on a cleaned glass slide. Scanning electron microscopy (SEM) image was captured with a Zeiss Evo series SEM model EVO 50. The sample was then coated in a sputter coater (EMITECH K 550 x) with a gold layer in vacuum.

Single-crystal X-ray data of compounds was collected on Bruker SMART CCD-Diffractometer using graphite monochromated Mo$K\alpha$ 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 $F2$ 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 ORTEP 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.

TEM analyses were performed on Delong instrument, Q imaging Retiga 4000 R by dropping 10µL of dispersed solution in HPLC grade hexane on copper grid. High resolution transmission electron microscope (HRTEM) experiments were conducted in a JEM-2010 FEI TEM with an accelerating voltage of 200 KV. UV-vis spectroscopy was recorded on Lambda Bio 20, Perkin Elmer. X-ray photoelectron spectroscopy (XPS) was carried out on SPECS, MCD-9, serial number-172-05.01.

Analytical Information:

All the isolated compounds were characterized by ^{1}H NMR, ^{13}C NMR spectroscopy and HRMS using $CDCl_3$, D_2O 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 air in septum covered oven dried round bottom flask/10 mL vial. All the solvents were bought from Aldrich, Spectrochem and Alfa-aesar were used as received. 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).