SYNTHESIS AND USE OF SOME IMIDAZOLIDINONE DERIVATIVES AND RELATED COMPOUNDS

BY

RAVI. VIJAYA KRISHNA

Submitted

in fulfillment of the requirements of the degree of

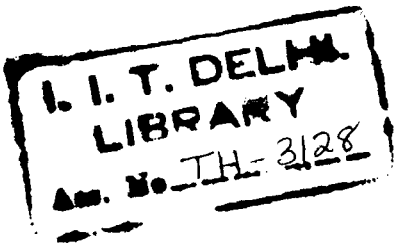
DOCTOR OF PHILOSOPHY

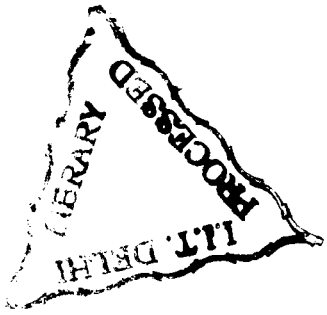
to the

Department of Chemistry

INDIAN INSTITUTE OF TECHNOLOGY, DELHI

DECEMBER, 2004


I. I. T. DELHI
LIBRARY
Acc. No. TH-3128


I.I.T. DELHI
PROCESSED
LIBRARY

CERTIFICATE

This is to certify that the thesis entitled **"Synthesis and Use of Some Imidazolidinone Derivatives and Related Compounds"** being submitted by Mr. R. Vijaya Krishna to the Indian institute of technology, Delhi, for the award of degree of Doctor of Philosophy in chemistry, is a record of bonafide research work carried out by him. Mr. R. Vijaya Krishna 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 in full, to any other University or Institute for the award of any degree or diploma.

Date: 31.12.04

Prof. U. K. NADIR
Department of Chemistry
Indian Institute of Technology Delhi
New Delhi – 110 016
INDIA

Acknowledgements

I wish to express my deep sense of gratitude and respect to **Prof. Upender K. Nadir** for his patience, understanding, and guidance throughout the course of this work.

I wish to express sincere thanks to Prof. M. N. Gupta, Prof. H. M. Chawla, Prof. B. Jayaram Prof. A. K. Singh and Dr. A. Ramanan for providing necessary facilities.

I would like to thank Prof. M. S. Hundal (Department of Chemistry, Guru Nanak Dev University) for carrying out x-ray studies.

My sincere thanks are due to Mr. Rama Rao, Dr. Vidya Sagar Swamy, Mr. A. Rangarao, Mr. T. Srinivas Rao, Mrs. Anamika Singh, Dr. S. Joshi, Mr. Vikas, Ms. Jaya, Mrs. Sarika, Mr. Shailesh, Mr. S. Sasi Kiran, Mr. R. Srinivas, Mr. P. Babu Dayal, Mr. Vamsi Krishna, Mr. P. Raghavendra Kumar, Mr. C. Sudhakhar Babu, Dr. A. Venu Gopal, Dr. I. Charles, Dr. Nabin K. Meher, Dr. Arif Ali Khan and other colleagues for their help and support.

I wish to express my deep sense of gratitude to my Parents and my wife for their help, patience understanding and immense support without which this work would never have been possible. My humble regards are due to my family members for their encouragement, especially my brother Radha Krishna for encouraging me throughout my research work.

I would also like to thank the technical staffs of Glass Blowing, Instrument, and NMR Laboratories for their kind cooperation.

Finally, I am thankful to CSIR for the financial support to carry out this research work.

(R. Vijaya Krishna)

Abstract

The investigations described in this dissertation were undertaken as part of a programme to develop synthetic methods based on three-membered heterocycles particularly aziridines. One of the methods developed in our laboratory, elaborated N-arylsulfonylaziridines to the corresponding 2-imidazolidinones through reaction with alkyl and aryl isocyanates in the presence of sodium or lithium iodide. In the present work attempts were made to extend this procedure to access 2-imidazolidinones bearing a functional group. One of the useful functionalities which lends itself to ready manipulation is the ester group. So N-arylsulfonylaziridines having an ester substituent were prepared by reacting an appropriately substituted methyl cinnamate with $PhI{=}NSO_2Ar$ in the presence of copper triflate according to Evan's method. These on reaction with phenyl isocyanate gave the expected 2-imidazolidinones. The reactions were found to be stereo-selective since the trans-aziridines gave only the trans-imidazolidinones. Reactions with cis-aziridines were not attempted since it had been observed by us and others before that the cis-aziridines either do not react with such nucleophiles or the reactions are very sluggish. The regiochemistry was also investigated and it was found that usually the iodide ion attacks the aziridine carbon bearing the phenyl group. However, with a p-nitro group on the phenyl ring, an almost 50:50 mixture of the two regio-isomers was obtained. This rather surprising result has been rationalized on the basis of Hard & Soft Acid Base concept (HSAB).

Attempts to extend this procedure to the synthesis of imidazolidinones bearing a ketonic functionality were unsuccessful. N-arylsulfonylaziridines bearing a benzoyl

group when subjected to treatment with phenyl isocyanate and LiI did not give the corresponding imidazolidinone and only an olefin was isolated. An explanation has been offered for this.

Another major goal of these studies was to use this methodology to access chiral 1,2-diamines. The strategy was to react the appropriate aziridine with an optically active isocyanate, separate the diastereomers and covert these individually to the corresponding diamines. Towards this end, 2-phenyl-N-p-toluenesulfonylaziridine was reacted with the commercially available R(+)-α-phenylethyl isocyanate and the diastereomeric mixture separated by fractional crystallization. Two steps (i) detosylation of imidazolidinone and (ii) removal of the phenylethyl group & cleavage of the ring were required to convert the 2-imidazolidinone to the corresponding diamine. Several reagents like Na-liq. NH_3, sod-naphthalenide, TBAF, SmI_2, Mg-MeOH were tried on model 2-imidazolidinones lacking chirality; the last one was found to be the best. The chiral diastereomers were separately treated with Mg-MeOH and the corresponding detosylated products obtained in excellent yield. The next step could be easily carried out by boiling with conc. HCl to obtain both enantiomers of 1-Phenyl-1,2-diaminoethane in the form of hydrochloride salts. Since the optical rotations for these could not be recorded under the reported conditions, they were converted to the ditosyl derivatives through treatment with p-toluenesulfonyl chloride. Both enantiomers of the ditosyl derivatives were obtained in better than 98% enantiomeric excess.

The same methodology was employed to convert 2-methyl-N-p-toluenesulfonylaziridine to the corresponding chiral diamine. Since optical rotation of the free diamines was known so derivatisation in this case was unnecessary. In this way both enantiomers of 1,2-diaminopropane could be obtained in greater than 98% enantiomeric excess.

Glossary of Symbols and Abbreviations

Ac	acetyl
aq.	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
BOC	tert-Butoxycarbonyl
Bu	butyl
BuLi	n-butyllithium
CHN	Carbon Hydrogen Nitrogen
Cat.	catalytic
Chem. Abstr.	Chemical Abstract
δ	Chemical shift
Conc.	Concentrated
J	Coupling constant
Cy	cyclohexyl
^{o}C	degree centigrade
DMF	N,N-dimethylformamide
DMSO	Dimethylsulphoxide
d	doublet
dd	doublet of doublets
eV	electron Volt
Et	Ethyl
EtOAc	Ethyl Acetate

Eq.	Equation
Fig.	Figure
e.g.	for example
g	gram
Hz	Hertz
h	hour
IR	Infrared
Lit.	Literature
LDA	Lithium diisopropylamide
m/z	mass/charge
MS	Mass Spectroscopy
MHz	mega Hertz
m.p.	melting point
Me	Methyl
ml	milliliter
mmol	milli mol
min.	minutes
mol	mole
M^+	molecular ion
m	multiplet
NMR	Nuclear Magnetic Resonance
p	para
ppm	parts per million
%	percent
cm^{-1}	per centimeter

Ph	phenyl
Pr	propyl
q	quartet
r.b.	round bottom
rt	room temperature
s	singlet
THF	Tetrahydrofuran
TLC	Thin layer chromatography
t	triplet
UV	ultra violet
*	D_2O exchangeable impurity probably arising from the solvent

CONTENTS