

NAME REACTIONS in HETEROCYCLIC CHEMISTRY

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Name Reactions in Heterocyclic Chemistry

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A JOHN WILEY & SONS, INC., PUBLICATION

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Published by John Wiley & Sons, Inc., Hoboken, New Jersey.

Published simultaneously in Canada.

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Library of Congress Cataloging-in-Publication Data is available.

ISBN 0-471-30215-5

Printed in the United States of America.

10 9 8 7 6 5 4 3 2 1

**Name Reactions
in Heterocyclic Chemistry**

To Alexandra

Foreword

Part of the charm of synthetic organic chemistry derives from the vastness of the intellectual landscape along several dimensions. First, there is the almost infinite variety and number of possible target structures that lurk in the darkness, waiting to be made. Then, there is the vast body of organic reactions that serve to transform one substance into another, now so large in number as to be beyond credibility to a non-chemist. Further, there is the staggering range of reagents, reaction conditions, catalysts, elements and techniques that must be mobilized in order to tame these reactions for synthetic purposes. Finally, it seems that new information is being added to the science at a rate that outstripped our ability to keep up with it. In such a troubled setting any author, or group of authors, must be regarded as heroic if, through their efforts, the task of the synthetic chemist is eased.

The field of heterocyclic chemistry has long presented a special problem for chemists. Because of its enormous information content and variety, it is not well taught to chemistry undergraduate or graduate students, even in simplified form. There is simply too much material for the time available. And yet, the chemistry of heterocyclic compounds and methods for their synthesis form the bedrock of modern medicinal chemical and pharmaceutical research. It is important for medicinal chemists to be broadly knowledgeable across a wide swath of heterocyclic chemistry. Those who specialize narrowly do so at their own peril. If you grant me the accuracy of all of the above, you likely will share my conviction that there is a need for high-quality, up-to-date, and authoritative books on heterocyclic synthesis that are helpful for the professional research chemist and also the advanced student. This volume, *Name Reactions in Heterocyclic Chemistry* is a model of what such books should be. Written concisely and with great skill and care by Dr. Jie Jack Li and a distinguished group of experts in the field of heterocyclic chemistry, this is a book that will be tremendously useful and helpful to synthetic and medicinal chemists, on whose shelves it will surely find a place. On behalf of these users, myself included, I send thanks and congratulations.



E. J. Corey
May 1, 2004

Preface

Since the infancy of organic chemistry, the practitioners in the field have often associated reactions with the chemists who discovered it. Even with the advent of IUPAC nomenclature, name reactions are still intimately intertwined with our profession, becoming a part of our daily language. Therefore, getting acclimated with this jargon is an integral part of the training to earn proficiency in organic chemistry.

On the other hand, heterocycles are of paramount importance to medicinal and agricultural chemists. This comprehensive and authoritative treatise provides a one-stop repository for name reactions in heterocyclic chemistry. Each name reaction is summarized in seven sections:

1. Description;
2. Historical Perspective;
3. Mechanism;
4. Variations and Improvements;
5. Synthetic Utility;
6. Experimental; and
7. References.

I also have introduced a symbol [R] to highlight review articles, book chapters and books dedicated to the respective name reactions.

I have incurred many debts of gratitude to Prof. E. J. Corey of Harvard University, who envisioned this project in the summer of 2002. What he once told me:—*“The desire to learn is the greatest gift from God.”*—has been a true inspiration. Furthermore, it has been my greatest privilege as well as a pleasure to work with a stellar collection of contributing authors from both academia and industry. Some of them are world-renowned scholars in the field; some of them have worked intimately with the name reactions that they have written; some of them even took part in the discovery of the name reactions that they authored in this manuscript. As a consequence, this book truly represents the state-of-the-art for *Name Reactions in Heterocyclic Chemistry*. We will follow up with the second volume to complete the series on heterocyclic chemistry.



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Acronyms and Abbreviations

))))	ultrasound
	polymer support
Ac	acetyl
AcOH	acetic acid
ADP	adenosine diphosphate
AE	asymmetric epoxidation reaction
AFO	Algar–Flynn–Oyamada
AIBN	2,2'-azobisisobutyronitrile
Alpine-borane [®]	<i>B</i> -isopinocampheyl-9-borabicyclo[3.3.1]-nonane
AME	acetyl malonic ester
AMNT	aminomalononitrile <i>p</i> -toluenesulfonate
Ar	aryl
ATP	adenosine triphosphate
AUC	area under curve
B:	generic base
9-BBN	9-borabicyclo[3.3.1]nonane
BFO	benzofurazan oxide
TBHP	<i>tert</i> -butyl hydrogen peroxide
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
Bn	benzyl
Boc	<i>tert</i> -butyloxycarbonyl
BOP	benzotriazol-1-yloxy-tris(dimethylamino)-phosphonium hexafluorophosphate
BPO	benzoyl peroxide
Bu	butyl
BZ reaction	Barton–Zard reaction
CAN	ceric ammonium nitrate (ammonium cerium(IV) nitrate)
CTAB	cetyl trimethylammonium bromide
CB-1	cannabinoid receptor-1
Cbz	benzyloxycarbonyl
CNS	central nervous system
COX-2	cyclooxygenase II
CSA	camphorsulfonic acid
CuTC	copper thiophene-2-carboxylate
DABCO	1,4-diazabicyclo[2.2.2]octane
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCB	dichlorobenzene
DCC	1,3-dicyclohexylcarbodiimide
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	diethyl azodicarboxylate
DEPC	diethyl phosphorocyanidate
DET	diethyl tartrate
Δ	solvent heated under reflux

DIC	diisopropylcarbodiimide
DHPM	3,4-dihydropyrimidin-2(1 <i>H</i>)-one
(DHQ) ₂ -PHAL	1,4-bis(9- <i>O</i> -dihydroquinine)-phthalazine
(DHQD) ₂ -PHAL	1,4-bis(9- <i>O</i> -dihydroquinidine)-phthalazine
DHT	5 α -dihydrotestosterone
DIBAL	diisobutylaluminum hydride
DMA	<i>N,N</i> -dimethylacetamide
DMA	<i>N,N</i> -dimethylaniline
DMAP	<i>N,N</i> -dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMFDMA	dimethylaminoformaldehyde dimethyl acetal
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
DMSY	dimethylsulfoxonium methylide
DMT	dimethoxytrityl
DNA	deoxyribonucleic acid
DNP	2,4-dinitrophenyl
<i>L</i> -DOPA	3,4-dihydroxyphenylalanine
dppb	1,4-bis(diphenylphosphino)butane
dppe	1,2-bis(diphenylphosphino)ethane
dppf	1,1'-bis(diphenylphosphino)ferrocene
dppp	1,3-bis(diphenylphosphino)propane
E1	unimolecular elimination
E2	bimolecular elimination
E1cb	2-step, base-induced β -elimination <i>via</i> carbanion
EDG	electron donating group
<i>ee</i>	enantiomeric excess
EMME	ethoxymethylenemalonate
<i>ent</i>	<i>enantiomer</i>
EPP	ethyl polyphosphate
Eq	equivalent
Et	ethyl
EtOAc	ethyl acetate
EPR (= ESR)	electron paramagnetic resonance spectroscopy
ESR (= EPR)	electronic spin resonance
EWG	electron withdrawing group
FMO	frontier molecular orbital
FVP	flash vacuum pyrolysis
GABA	γ -aminobutyric acid
GC	gas chromatography
GC reaction	Gabriel-Colman reaction
H	hours
His	histidine
HIV	human immunodeficiency virus
HMDS	hexamethyldisilazine

HMPA	hexamethylphosphoric triamide
HOMO	highest occupied molecular orbital
HPLC	high performance liquid chromatography
IBCF	isobutylchloroformate
Imd	imidazole
IPA	isopropanol
<i>i</i> -Pr	isopropyl
KCO	potassium channel opener
KHMDS	potassium hexamethyldisilazide
KR	Kostanecki–Robinson
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium hexamethyldisilazide
LiHMDS	lithium hexamethyldisilazide
LTMP	lithium 2,2,6,6-tetramethylpiperidine
LUMO	lowest unoccupied molecular orbital
M	metal
M	moles per liter (molar)
MCR	multi-component reaction
<i>m</i> -CPBA	<i>m</i> -chloroperoxybenzoic acid
Me	methyl
Mes	mesityl
mL	milliliters
MMPP	magnesium monoperoxyphthalate hexahydrate
mmol	millimoles
MO	molecular orbital
MOA	mechanism of action
MOM	methoxymethyl
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
MVK	methyl vinyl ketone
MWI (μv)	microwave irradiation
NAD ⁺	nicotinamide adenine dinucleotide (oxidized form)
NADH	nicotinamide adenine dinucleotide
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NIS	<i>N</i> -iodosuccinimide
NMDA	<i>N</i> -methyl-D-aspartate
NMO	<i>N</i> -methylmorpholine- <i>N</i> -oxide
NMP	1-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
Nu	nucleophile
NPY	neuropeptide Y
NSAIDs	non-steroidal anti-inflammatory drugs
OA	osteoarthritis
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate

PDE	phosphodiesterase
PG	prostaglandin
pGlu	pyroglutamic acid
Ph	phenyl
PK	pharmacokinetics
pKa	–Log acidity constant
PKC	protein kinase C
PPA	polyphosphoric acid
PPE	polyphosphate ester
PPI	proton pump inhibitor
4-PPNO	4-phenylpyridine- <i>N</i> -oxide
PPP	3-(3-hydroxyphenyl)-1- <i>n</i> -propylpiperidine
PPSE	polyphosphoric acid trimethylsilyl ester
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pro	proline
PSI	pounds per square inch
PTC	phase transfer catalyst
PTSA	paratoluenesulfonic acid
Py	pyridine
Pyr	pyridine
RA	rheumatoid arthritis
RNA	ribonucleic acid
rt	room temperature
Salen	<i>N,N'</i> -disalicylidene-ethylenediamine
SET	single electron transfer
S _N Ar	nucleophilic substitution on an aromatic ring
S _N 1	unimolecular nucleophilic substitution
S _N 2	bimolecular nucleophilic substitution
<i>t</i> -Bu	<i>tert</i> -butyl
TBAF	tetrabutylammonium fluoride
TBD	1,5,7-triazabicyclo[4.4.0]dec-5-ene
TBDMS	<i>tert</i> -butyldimethylsilyl
TBDPS	<i>tert</i> -butyldiphenylsilyl
TBHP	<i>tert</i> -butylhydroperoxide
TBS	<i>tert</i> -butyldimethylsilyl
TEA	triethylamine
Tf	trifluoromethanesulfonyl (triflic)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TfOH	triflic acid
TFP	tri- <i>o</i> -furylphosphine
TFSA	trifluorosulfonic acid
THF	tetrahydrofuran
THIP	4,5,6,7-tetrahydroisoxazolo[5,4- <i>c</i>]pyridin-3-ol
TIPS	triisopropylsilyl
TLC	thin layer chromatography

TMEDA	<i>N,N,N',N'</i> -tetramethylethylenediamine
TMG	tetramethylguanidine
TMP	tetramethylpiperidine
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSCN	trimethylsilyl cyanide
TMSI	trimethylsilyl iodide
TMSOTf	trimethylsilyl triflate
Tol	toluene or tolyl
Tol-BINAP	2,2'-bis(di- <i>p</i> -tolylphosphino)-1,1'-binaphthyl
TosMIC	(<i>p</i> -tolylsulfonyl)methyl isocyanide
TPAP	tetra- <i>n</i> -propylammonium perruthenate
TRH	thyrotropin releasing hormone
Ts	<i>p</i> -toluenesulfonyl (tosyl)
TSA	<i>p</i> -toluenesulfonic acid
TsO	tosylate

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