

# Heterocyclic Chemistry at a Glance

Second Edition

John A. Joule  
Keith Mills

 WILEY

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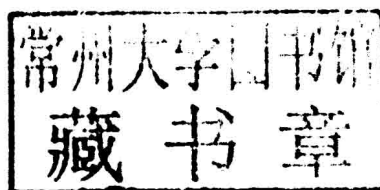
Second Edition

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 **WILEY**

A John Wiley & Sons, Ltd., Publication

This edition first published 2013  
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John Wiley & Sons Ltd, The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, United Kingdom

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*Library of Congress Cataloging-in-Publication Data*

Joule, J. A. (John Arthur)

Heterocyclic chemistry at a glance / John Joule, Keith Mills. – 2nd ed.

p. cm.

Includes index.

ISBN 978-0-470-97122-2 (cloth) – ISBN 978-0-470-97121-5 (pbk.) 1. Heterocyclic chemistry–Textbooks

2. Chemistry–Textbooks. I. Mills, K. (Keith) II. Title.

QD400.J594 2012

547'.59–dc23

2012016201

A catalogue record for this book is available from the British Library.

Cloth ISBN: 9780470971222

Paper ISBN: 9780470971215

Set in 10/12.5pt Minion by Thomson Digital, Noida, India

Printed and bound in Singapore by Markono Print Media Pte Ltd

Answers to the exercises are available on the accompanying website <http://booksupport.wiley.com>

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# Biography

**John Arthur Joule** was born in Harrogate, Yorkshire, England, but grew up and attended school in Llandudno, North Wales, going on to study for BSc, MSc, and PhD (1961; with George F. Smith) degrees at The University of Manchester. Following post-doctoral periods in Princeton (Richard K. Hill) and Stanford (Carl Djerassi) he joined the academic staff of The University of Manchester where he served for 41 years, retiring and being appointed Professor Emeritus in 2004. Sabbatical periods were spent at the University of Ibadan, Nigeria, Johns Hopkins Medical School, Department of Pharmacology and Experimental Therapeutics, and the University of Maryland, Baltimore County. He was William Evans Visiting Fellow at Otago University, New Zealand.

Dr. Joule has taught many courses on heterocyclic chemistry to industry and academe in the UK and elsewhere. He is currently Associate Editor for *Tetrahedron Letters*, Scientific Editor for *Arkivoc*, and Co-Editor of the annual *Progress in Heterocyclic Chemistry*.

**Keith Mills** was born in Barnsley, Yorkshire, England and attended Barnsley Grammar School, going on to study for BSc, MSc and PhD (1971; with John Joule) degrees at The University of Manchester.

Following post-doctoral periods at Columbia (Gilbert Stork) and Imperial College (Derek Barton/Philip Magnus), he joined Allen and Hanburys (part of the Glaxo Group) at Ware and later Stevenage (finally as part of GSK), working in Medicinal Chemistry and Development Chemistry departments for a total of 25 years. During this time he spent a secondment at Glaxo, Verona. Since leaving GSK he has been an independent consultant to small pharmaceutical companies.

Dr. Mills has worked in several areas of medicine and many areas of organic chemistry, but with particular emphasis on heterocyclic chemistry and the applications of transition metal-catalysed reactions.

*Heterocyclic Chemistry* was first published in 1972, written by George Smith and John Joule, followed by a second edition in 1978. The third edition (Joule, Mills and Smith) was written in 1995 and, after the death of George Smith, a fourth edition (Joule and Mills) appeared in 2000 and a fifth edition in 2010. The first edition of *Heterocyclic Chemistry at a Glance* was published in 2007.

# Abbreviations

Ac	acetyl [ $\text{CH}_3\text{C}=\text{O}$ ], thus $\text{AcOH}$ = ethanoic (acetic) acid; $\text{Ac}_2\text{O}$ = ethanoic anhydride (acetic anhydride)
<i>anti</i>	on the opposite side (antonym of <i>syn</i> )
aq	aqueous – the reaction mixture contains water
Ar	general designation for a benzenoid aromatic group
[bmim][ $\text{BF}_4$ ]	1- <i>n</i> -butyl-3-methylimidazolium tetrafluoroborate (an ionic liquid)
BINAP	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl – ligand for palladium(0)
Bn	benzyl [ $\text{PhCH}_2$ ] – <i>N</i> -protecting group; removed by hydrogenolysis over Pd
Boc	<i>t</i> -butoxycarbonyl [ $t\text{-BuOCO}$ ] – protecting group; removed with acid
Bom	benzyloxymethyl [ $\text{PhCH}_2\text{OCH}_2$ ] – protecting group; removed by hydrogenolysis over Pd
Bt	benzotriazol-1-yl (structure page 136)
Bz	benzoyl [ $\text{PhCO}$ ] as in OBz, a benzoate
<i>c</i>	cyclo as in <i>c</i> - $\text{C}_6\text{H}_{11}$ = cyclohexyl
<i>c.</i>	concentrated, as in <i>c.</i> $\text{H}_2\text{SO}_4$ = concentrated sulfuric acid
cat	catalyst – reagent not consumed in the reaction – usually, in the case of metal catalysts, e.g. Pd, used in sub-stoichiometric quantities – 1–5 mol%
Cbz	benzyloxycarbonyl [ $\text{PhCH}_2\text{OCO}$ ] – protecting group; removed by hydrogenolysis
CDI	1,1'-carbonyldiimidazole [ $(\text{C}_3\text{H}_3\text{N}_2)_2\text{C}=\text{O}$ ] – peptide coupling reagent
Cy	cyclohexyl [ <i>c</i> - $\text{C}_6\text{H}_{11}$ ]
dba	<i>trans,trans</i> -dibenzylideneacetone [ $\text{PhCH}=\text{CHCOCH}=\text{CHPh}$ ] – ligand for palladium(0)
DCC	dicyclohexylcarbodiimide [ <i>c</i> - $\text{C}_6\text{H}_{11}\text{N}=\text{C}=\text{Nc-C}_6\text{H}_{11}$ ] – for coupling acid and amine to give amide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone – oxidant, often used for dehydrogenation
DMAP	4-dimethylaminopyridine [ $4\text{-Me}_2\text{NC}_5\text{H}_4\text{N}$ ] – nucleophilic catalyst
DME	1,2-dimethoxyethane [ $\text{MeO}(\text{CH}_2)_2\text{OMe}$ ] – ethereal solvent
DMF	dimethylformamide [ $\text{Me}_2\text{NCH}=\text{O}$ ] – dipolar aprotic solvent
DMFDMA	dimethylformamide dimethyl acetal [ $\text{Me}_2\text{NCH}(\text{OMe})_2$ ]
DMSO	dimethylsulfoxide [ $\text{Me}_2\text{S}=\text{O}$ ] – dipolar aprotic solvent
dppb	1,4-bis(diphenylphosphino)butane [ $\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2$ ] – ligand for palladium(0)
dppe	1,2-bis(diphenylphosphino)ethane [ $\text{Ph}_2\text{P}(\text{CH}_2)_2\text{PPh}_2$ ] – ligand for palladium(0)
dppf	1,1'-bis(diphenylphosphino)ferrocene [ $(\text{Ph}_2\text{PC}_5\text{H}_4)_2\text{Fe}$ ] – ligand for palladium(0)
dppp	1,3-bis(diphenylphosphino)propane [ $\text{Ph}_2\text{P}(\text{CH}_2)_3\text{PPh}_2$ ] – ligand for palladium(0)
ee	enantiomeric excess – a measure of the efficiency of an asymmetric synthesis
$\text{El}^+$	general designation for a positively charged electrophile
Et	ethyl [ $\text{CH}_3\text{CH}_2$ ]
<i>f.</i>	fuming, as in <i>f.</i> $\text{HNO}_3$ = fuming nitric acid
2-Fur	furan-2-yl [ $\text{C}_4\text{H}_3\text{O}$ ]
GABA	$\gamma$ -aminobutyric acid (4-aminobutanoic acid) [ $\text{H}_2\text{N}(\text{CH}_2)_3\text{CO}_2\text{H}$ ]
Hal	general designation for a halogen
Het	general designation for a heteroaryl group

<i>i</i> -Pr	isopropyl [ $\text{Me}_2\text{CH}$ ]
LDA	lithium di-isopropylamide [ $\text{LiN}(i\text{-Pr})_2$ ] – hindered strong base
LiTMP	lithium 2,2,6,6-tetramethylpiperidide [ $\text{LiN}(\text{C}(\text{Me})_2(\text{CH}_2)_3\text{C}(\text{Me})_2)$ ] – hindered non-nucleophilic strong base
Me	methyl [ $\text{CH}_3$ ]
Ms	methanesulfonyl (mesyl) [ $\text{MeSO}_2$ ] – protecting group for azole nitrogen
NaHMDS	sodium bis(trimethylsilyl)amide [sodium hexamethyldisilazide] [ $\text{NaN}(\text{SiMe}_3)_2$ ] – hindered non-nucleophilic strong base
NBS	<i>N</i> -bromosuccinimide [ $\text{C}_4\text{H}_4\text{BrNO}_2$ ] – brominating agent
NCS	<i>N</i> -chlorosuccinimide [ $\text{C}_4\text{H}_4\text{ClNO}_2$ ] – chlorinating agent
NMP	<i>N</i> -methylpyrrolidin-2-one (1-methylpyrrolidin-2-one) [ $\text{C}_5\text{H}_9\text{NO}$ ] – dipolar aprotic solvent
<i>n</i> -Bu	normal butyl [ $\text{CH}_3(\text{CH}_2)_3$ ]
<i>n</i> -Pr	normal propyl [ $\text{CH}_3\text{CH}_2\text{CH}_2$ ]
$\text{Nu}^-$	general designation for a negatively charged nucleophile
Ph	phenyl [ $\text{C}_6\text{H}_5$ ]
PMB	<i>p</i> -methoxybenzyl [ $4\text{-MeOC}_6\text{H}_4\text{CH}_2$ ]
Pr	see <i>i</i> -Pr and <i>n</i> -Pr
2-Py; 3-Py; 4-Py	pyridin-2-yl; pyridin-3-yl; pyridin-4-yl [ $\text{C}_5\text{H}_4\text{N}$ ]
R	general designation for an alkyl group
<i>o</i> -Tol	<i>ortho</i> -tolyl (2-methylphenyl) [ $\text{C}_7\text{H}_7$ ]
<i>p</i> -Tol	<i>para</i> -tolyl (4-methylphenyl) [ $\text{C}_7\text{H}_7$ ]
rt	room temperature (ca. 20 °C)
Selectfluor™	1-(chloromethyl)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane tetrafluoroborate – electrophilic fluorinating agent
SEM	trimethylsilylethoxymethyl [ $\text{Me}_3\text{Si}(\text{CH}_2)_2\text{OCH}_2$ ] – protecting group; removed with fluoride
SES	trimethylsilylethanesulfonyl [ $\text{Me}_3\text{Si}(\text{CH}_2)_2\text{SO}_2$ ] – <i>N</i> -protecting group; removed with fluoride
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxy-1,1'-biphenyl – ligand for palladium(0)
<i>syn</i>	on the same side (antonym of <i>anti</i> )
TBDMS	<i>t</i> -butyldimethylsilyl [ $t\text{-Bu}(\text{CH}_3)_2\text{Si}$ ] – bulky silyl protecting group
<i>t</i> -Bu	tertiary butyl [ $(\text{CH}_3)_3\text{C}$ ]
Tf	trifluoromethanesulfonyl [ $\text{CF}_3\text{SO}_2$ ], thus $\text{TfO}^- = \text{triflate}$ [ $\text{CF}_3\text{SO}_3^-$ ] – triflate is a good leaving group
THF	tetrahydrofuran – common ethereal solvent for dry reactions at low temperature
THP	tetrahydropyran-2-yl [ $\text{C}_5\text{H}_9\text{O}$ ] – protecting group; removed with aqueous acid
TIPS	tri-isopropylsilyl [ $\text{Si}(i\text{-Pr})_3$ ] – protecting group for nitrogen or oxygen
TIPB	1,3,5-tri- <i>iso</i> -propylbenzene – inert high-boiling solvent
TMSCl	trimethylsilyl chloride (chlorotrimethylsilane) [ $\text{Me}_3\text{SiCl}$ ] – <i>O</i> - and <i>N</i> -trimethylsilylating reagent
Tol	same as <i>p</i> -Tol
TosMIC	tosylmethyl isocyanide [ $\text{TolSO}_2\text{CH}_2\text{N}^+\equiv\text{C}^-$ ]
Ts	<i>p</i> -toluenesulfonyl (tosyl) [ $p\text{-TolSO}_2$ ] – Ts is a good protecting group for azole nitrogen and $\text{Ts}^-$ can be a leaving group ( <i>para</i> -toluensulfinate)
Tr	trityl (triphenylmethyl) [ $\text{Ph}_3\text{C}$ ] – <i>N</i> -protecting group; removed with acid
TTF	tetrathiafulvalene ( $\text{C}_6\text{H}_4\text{S}_4$ )
X	general designation for halogen (or in palladium(0) chemistry, sometimes OTf)



# Introduction to Second Edition

The material in this book comprises an introduction to, and summary of, the most important ideas and principles of heterocyclic chemistry. We have attempted to encapsulate everything that a non-specialist, or beginning student, would need to know of the subject. At the same time, we believe that this book will serve as a good starting point for further, more extensive study of the subject.

This Second Edition has been expanded by 50% compared with the First Edition (2007), allowing us to include more examples and illustrations, and exercises at the ends of the chapters (with answers available online at <http://booksupport.wiley.com>). The other significant difference to the First Edition is the use of colour in the schemes (for details, see below).

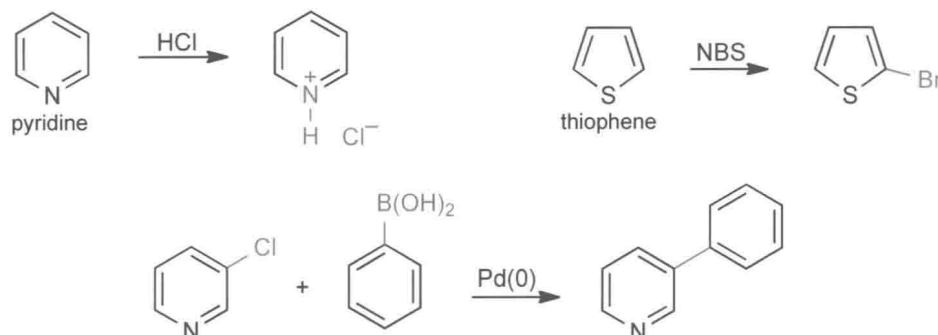
We now have three supplementary chapters dealing with the occurrence and significance of heterocycles in the world at large: Chapters 17 and 18 deal with 'Heterocycles in Nature' and 'Heterocycles in Medicine'; Chapter 19 discusses major significant heterocyclic involvements in dyes and pigments, polymers, pesticides, explosives, food and drink, and electronics.

The book is mainly concerned with aromatic heterocycles though we also include a short discussion of non-aromatic heterocycles (Chapter 16). We deal with the characteristic reactivities of the most important heteroaromatic systems and the principal routes for their ring synthesis from non-heterocyclic precursors. Thus the chemistry of pyridines, pyridazines, pyrimidines, pyrazines, quinolines, isoquinolines, pyrylium and benzopyrylium cations, pyrroles, indoles, thiophenes, furans, imidazoles, oxazoles, thiazoles, pyrazoles, isoxazoles, isothiazoles, purines, heterocycles with more than two heteroatoms in the ring (for example triazoles and triazines) and heterocycles in which a heteroatom is located at a ring junction (for example pyrrolizines and indolizines) is covered (Chapters 5–15). The book starts with a discussion of nomenclature and structures of aromatic heterocycles (Chapters 1 and 2); then follows Chapter 3, which examines in detail the typical reactions of heterocycles, except for those involving palladium-catalysis, since these are considered separately in the following Chapter 4.

The book assumes a basic knowledge of organic chemistry such as one would expect of a student at the second year level of a UK Honours Chemistry course and thus would be suitable for second/third/fourth year undergraduate and post-graduate courses in UK Universities. It is also relevant that much Inorganic Chemistry relies on maintaining metals in various (often unusual) oxidation states by surrounding them with ligands and that these are very often heterocyclic, so choosing or designing appropriate heterocyclic ligands and then being able to synthesise them, is also an integral prerequisite of Inorganic Chemistry. With this book we also target students in other disciplines – Pharmacy, Pharmacology, Medicinal Chemistry – whose subjects require them to assimilate the basics of this particular area of organic chemistry. The vital importance of a proper understanding of heterocyclic chemistry for the study of biochemistry at the molecular level and for drug design and synthesis in medicinal chemistry, is emphasised in Chapters 17 and 18, 'Heterocycles in Nature' and 'Heterocycles in Medicine'.

It is not the purpose of this book to provide guidance for the conduct of practical work: especially at the undergraduate level, all experimental work must be conducted under the supervision of an experienced teacher. For experimental details the reader must consult the original literature – many references to suitable, key papers can be found in our fuller exposition – *Heterocyclic Chemistry, 5<sup>th</sup> Edition*, Joule and Mills, Wiley, 2010. All the examples in *Heterocyclic Chemistry at a Glance* are taken from the literature and the vast majority proceed in good yields. In the reaction schemes, so that the reader can concentrate on the chemistry in question, we have simply shown that a particular compound will react with a particular reagent or reactant to give a product, and we have omitted practical details such as solvent, reaction time, yields, and most other details, except where their inclusion makes a didactical point. Where reactions were carried out at room temperature or with gentle warming or cooling, no comment is made. Where reactions were carried out with strong heating (e.g. reflux in a high-boiling solvent) the word 'heat' is used on the reaction arrow; for transformations carried out at very low temperature, this is specified on the reaction arrow. For some of the palladium-catalysed reactions we give full experimental conditions, to illustrate what is typical for cross-couplings.

In the reaction schemes, we have highlighted in red those parts of the products (or intermediates) where a change in structure or bonding has taken place. We hope that this both facilitates comprehension of the chemical processes that are occurring and quickly focuses the reader's attention on just those parts of the molecules where structural change has occurred. For example, in the first reaction below, only changes at the pyridine nitrogen are involved; in the second example, the introduced bromine resulting from the substitution, and its new bond to the heterocycle, are highlighted. The exception to this policy is in palladium-catalysed cross-coupling processes where the functional groups in each of the coupling partners, as well as the new bond formed, are coloured red, as shown in the third example below.



Finally we acknowledge the crucial advice, support and encouragement from staff at Wiley, in bringing this project to fruition, in particular Paul Deards and Sarah Tilley. Mrs Joyce Dowle is thanked for her helpful comments during the preparation of Chapter 19 and Judith Egan-Shuttler for her careful copy editing.

## Further reading

This book can act only as an introduction to heterocyclic chemistry and does not include references to original literature, or to the many reviews that are available. For further study and to go more deeply into the topics covered in this book we recommend, as a first port-of-call, our textbook *Heterocyclic Chemistry* [1] in which there are a host of leading references to the original literature and appropriate reviews.

The premier sources of regular reviews in this area are *Advances in Heterocyclic Chemistry* [2] and *Progress in Heterocyclic Chemistry* [3] and the principles of heterocyclic nomenclature are set out in one review [4] in the former series. The journal, *Heterocycles*, also carries many useful reviews specifically in the heterocyclic area. As its title implies, an exhaustive coverage of the area is provided in the three parts of *Comprehensive Heterocyclic Chemistry* (CHC), original (1984), and its two updates (1996 and 2008) [5]. Note: The three parts must be read *together* – the later parts update but do not repeat the earlier material. The *Handbook of Heterocyclic Chemistry* [6] that accompanies CHC encapsulates the key information from the series in a single volume. There is a comprehensive compilation of heterocyclic data and facts: the still-continuing and still-growing series of monographs [7] dealing with particular heterocyclic systems, edited originally by Arnold Weissberger, and latterly by Edward C. Taylor and Peter Wipf, is a vital source of information and reviews for all those working with heterocyclic compounds. The ‘*Science of Synthesis*’ series contains authoritative discussions on the synthesis of heterocycles, organized in a hierarchical system [8]; volumes 9–17, published over the period 2000–2008, discuss aromatic heterocycles.

For further reading relating in particular to Chapters 17, 18 and 19, we recommend *Heterocycles in Life and Society* [9], *Introduction to Enzyme and Coenzyme Chemistry* [10], *Nucleic Acids in Chemistry and Biology* [11], *The Alkaloids; Chemistry and Biology* [12], *Comprehensive Medicinal Chemistry II* [13], *Molecules and Medicine* [14], *Goodman and Gilman's The Pharmacological Basis of Therapeutics* [15], *The Chemistry of Explosives* [16], *Food. The Chemistry of its Components* [17], *Perfumes: the Guide* [18], *Handbook of Conducting Polymers* [19], *Handbook of Oligo- and Polythiophenes* [20], *Tetrathiafulvalenes, Oligoacenes, and their Buckminsterfullerene Derivatives: the Bricks and Mortar of Organic Electronics* [21].

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