BENZIMIDAZOLES AND CONGENERIC TRICYCLIC COMPOUNDS

PART 1

Edited by

P. N. PRESTON

DEPARTMENT OF CHEMISTRY,
HERIOT-WATT UNIVERSITY,
EDINBURGH, SCOTLAND

With contributions by

D. M. SMITH
DEPARTMENT OF CHEMISTRY,
UNIVERSITY OF ST. ANDREWS,
ST. ANDREWS,
SCOTLAND

G. TENNANT
DEPARTMENT OF CHEMISTRY,
UNIVERSITY OF EDINBURGH,
EDINBURGH,
SCOTLAND

AN INTERSCIENCE ® PUBLICATION

JOHN WILEY & SONS

New York . Chichester . Brisbane . Toronto

Benzimidazoles and Congeneric Tricyclic Compounds

IN TWO PARTS

PART ONE

This is the fortieth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

ARNOLD WEISSBERGER and EDWARD C. TAYLOR

Editors

BENZIMIDAZOLES AND CONGENERIC TRICYCLIC COMPOUNDS

PART 1

Edited by

P. N. PRESTON

DEPARTMENT OF CHEMISTRY,
HERIOT-WATT UNIVERSITY,
EDINBURGH, SCOTLAND

With contributions by

D. M. SMITH
DEPARTMENT OF CHEMISTRY,
UNIVERSITY OF ST. ANDREWS,
ST. ANDREWS,
SCOTLAND

G. TENNANT
DEPARTMENT OF CHEMISTRY,
UNIVERSITY OF EDINBURGH,
EDINBURGH,
SCOTLAND

AN INTERSCIENCE ® PUBLICATION

JOHN WILEY & SONS

New York . Chichester . Brisbane . Toronto

An Interscience ® Publication

Library of Congress Cataloging in Publication Data:
Main entry under title:

Benzimidazoles and congeneric tricyclic compounds.

(The Chemistry of heterocyclic compounds;
-v. 40, pt. 1 ISSN 0069-3154)
"An Interscience publication."
Includes index
1. Benzimidazoles. I. Preston, P. N.
QD401.B46 547'.593 80-17383
ISBN 0-471-03792-3 (v. 1)
ISBN 0-471-08189-2 (v. 2)

The Chemistry of Heterocyclic Compounds

The chemistry of heterocyclic compounds is one of the most complex branches of organic chemistry. It is equally interesting for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocyclic compounds.

A field of such importance and intrinsic difficulty should be made as readily accessible as possible, and the lack of a modern detailed and comprehensive presentation of heterocyclic chemistry is therefore keenly felt. It is the intention of the present series to fill this gap by expert presentations of the various branches of heterocyclic chemistry. The subdivisions have been designed to cover the field in its entirety by monographs which reflect the importance and the interrelations of the various compounds, and accommodate the specific interests of the authors.

In order to continue to make heterocyclic chemistry as readily accessible as possible, new editions are planned for those areas where the respective volumes in the first edition have become obsolete by overwhelming progress. If, however, the changes are not too great so that the first editions can be brought up-to-date by supplementary volumes, supplements to the respective volumes will be published in the first edition.

ARNOLD WEISSBERGER

Research Laboratories
Eastman Kodak Company
Rochester, New York

EDWARD C. TAYLOR

Princeton University
Princeton, New Jersey

Preface to Part 1

More than 25 years have elapsed since the publication in this series of *Imidazole and Its Derivatives* by Klaus Hofmann. In updating this work, Leroy Townsend has undertaken the task of editing a volume on monocyclic imidazoles, and the present book covers the chemistry of benzimidazole and its dihydro derivatives, as well as congeneric tricyclic compounds that contain a condensed benzimidazole moiety. Because many ring systems are covered, it has proved necessary to divide the volume into Part 1 (Chapters 1 to 5) and Part 2 (Chapters 6 to 10).

Chapters 1 to 3 on benzimidazoles, benzimidazole *N*-oxides, and dihydro derivatives update the book of Hofmann through Volume 87 of *Chemical Abstracts*. The chemistry of tricyclic compounds containing a condensed benzimidazole moiety is covered comprehensively from early literature through the same Volume 87 of *Chemical Abstracts*.

Chapters 4 to 9 on the condensed ring systems are organized in terms of the position and size of the ring fused to the benzimidazole skeleton (denoted "6-5"). Thus Chapters 4 through 8 are concerned with compounds in which fusion of the third ring is at the benzo and imidazole rings respectively.

Chapter 9 deals with the chemistry of tricyclic compounds in which a benzimidazole moiety may be considered to be formally annulated from N-1 to C-7.

The growth of benzimidazole chemistry in the past 25 years has paralleled that of purines and stems from the determination of the partial structures of nucleic acids in the early 1950s. Benzimidazoles and congeneric compounds are substrates that might act as inhibitors in nucleic acid biosynthesis, and their relative ease of preparation and low cost make them attractive as potential pharmacological agents. The variety of marketed products described in chapter 10 bears witness to the large commitment to benzimidazole chemistry. I hope that this book will stimulate further research, particularly on the synthesis of new tricyclic derivatives and related condensed analogs.

I am indebted to a number of friends and colleagues who have contributed to this book. It has been a pleasure to collaborate with David Smith and with Malcolm Stevens and George Tennant, and I thank them for their large collective contribution. Information on commercially marketed products is difficult to obtain, but my task was simplified with the generous assistance of Colin C. Beard, Gerald Farrow, Janet M. Shether, Brian K. Snell, and Ian S. Swanson. I also thank my wife, Veronica, who carried out an initial estimate of the magnitude of literature on benzimidazoles and

congeneric tricyclic compounds. Thanks are due also to Susan Bobby who typed part of the manuscript, Anthony F. Fell who translated a number of documents from Russian, and my former research students Alex Davidson and Ian E. P. Murray who helped to check the manuscript. Finally, I express my appreciation of the help and enthusiasm of the Series Editors, Edward C. Taylor and Arnold Weissberger, of Stanley F. Kudzin, and of the staff of John Wiley and Sons, Inc.

P. N. PRESTON

Edinburgh, Scotland
January 1981

Contents

PART ONE

PART TWO

Benzimidazoles and Congeneric Tricyclic Compounds

IN TWO PARTS

PART ONE

This is the fortieth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

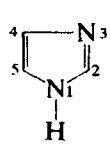
CHAPTER 1

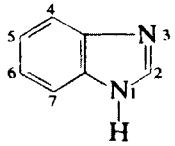
Benzimidazoles

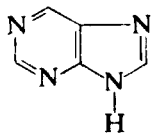
P. N. PRESTON

1.1. INTRODUCTION: LITERATURE COVERAGE AND ORGANIZATION OF THE BOOK

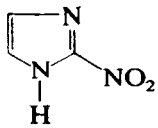
In 1953 the extent of the literature was such that Klaus Hofmann was able to comprehensively cover the entire chemistry of monocyclic imidazoles (**1.1**) and benzimidazoles (**1.2**) in *Imidazole and Its Derivatives, Part I.*[1]

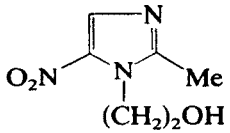

(**1.1**)

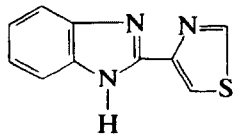

(**1.2**)

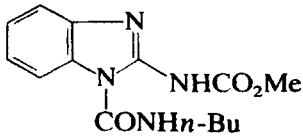

(**1.3**)

The early 1950s was an important period regarding the biological significance of benzimidazoles and the closely related purines (**1.3**);[2] the vital role of purines in biological systems was established,[2] and it was discovered that 5,6-dimethyl-1-(α-D-ribofuranosyl)benzimidazole is an integral part of the structure of vitamin B_{12}.[3] These findings stimulated great interest in the chemistry of imidazoles and related compounds, and considerable commercial success has accrued from these studies: a new antibacterial agent [azomycin (**1.4**)],[4] a trichomonacide [metronidazole (**1.5**)],[5] and a variety of benzimidazole derivatives of use as anthelmintic agents [e.g., thiabendazole (**1.6**)] and fungicides [e.g., benomyl (**1.7**)] are well-established marketed products (see also Chapter 10).


(**1.4**)


(**1.5**)


(**1.6**)


(**1.7**)

Systematic reviews on benzimidazoles appeared in 1951,[6] 1953,[1] and 1974,[7] although surveys have appeared in articles[8–10] covering the chemistry of both imidazoles and benzimidazoles. The chemistry of benzimidazole *N*-oxides has been covered in the texts of Ochiai[11] and Katritzky and Lagowski[12] and also in a short review by Lettau.[13] Specific synthetic procedures leading to benzimidazoles and benzimidazole *N*-oxides based on

the use of *ortho*-substituted nitrobenzene derivatives have been described,[14] and methods employing *ortho*-substituted *tert*-alkylanilines have been reviewed.[15]

The magnitude of the literature on benzimidazoles presents a difficult problem for a reviewer. In the twenty-five-year period since publication of Hofmann's book[1] there have been approximately 25,000 *Chemical Abstracts* compound citations on benzimidazoles; by comparison it is interesting to note that Lister's text[2] in this series refers to 3000 citations on purines from the origin of such studies through 1970. Accordingly no attempt has been made in this chapter to provide comprehensive physicochemical data (e.g., mp, bp) on all cited benzimidazole derivatives. Nevertheless, the chapter is comprehensive in the sense that relevant publications appearing in *Chemical Abstracts* subsections on imidazoles are included (Volumes 48 through 78); material has also been selectively abstracted from the subject index, but the chemistry of benzimidazole nucleosides[16] and transition metal organometallic complexes of benzimidazoles is excluded.

The subject matter in Part 1 (Chapters 1 to 5) and Part 2 (Chapters 6 to 10) is organized in terms of synthesis, physicochemical properties, and reactions; synthetic methods are described in terms of the types of starting materials employed, and the sections on reactions are categorized on a mechanistic basis rather than on product type. The appended tables of data at the end of this chapter contain comprehensive lists of benzimidazole derivatives categorized according to functional group type.

Benzimidazole *N*-oxides (Chapter 2) and dihydrobenzimidazoles (Chapter 3) are treated separately, and condensed benzimidazoles are organized according to the size and position of fusion of the condensed ring. Using a 6-5 notation for benzimidazole, chapters on condensed compounds are included in which fusion is on the benzo ring [5-6-5 and 6-6-5 systems (Chapters 4 and 5)] or on the imidazole ring [6-5-5, 6-5-6, 6-5-7, and higher (Chapters 6 to 8)]; the chemistry of compounds that are annulated from positions 1 to 7 of a benzimidazole ring is discussed in Chapter 9.

An attempt has been made in Chapter 10 to present data on benzimidazoles (including dihydro derivatives) that have been marketed commercially in the last decade.

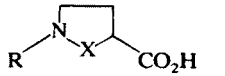
1.2. SYNTHESIS OF BENZIMIDAZOLES

1.2.1. From Reactions of *o*-Arylenediamines with:

Carboxylic Acids

Synthetic methods leading to benzimidazoles (Table 1.1)[17–110] and bisbenzimidazoles[28,111–129] (Table 1.2) from the reaction of *o*-arylenediamines and mono- or dicarboxylic acids are widely applicable. In

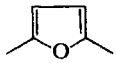
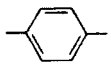
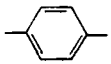
TABLE 1.1. SYNTHESIS OF BENZIMIDAZOLES BY THE REACTION OF *o*-ARYLENEDIAMINES WITH CARBOXYLIC ACIDS

Carboxylic acid	Ref.
H—CO_2H	17–35
H—$^{14}CO_2H$	36
CH_3CO_2H	18, 22, 23, 25, 27 32–35, 37, 38, 39
R—CO_2H (R = alkyl, adamantyl)	40[b]
$ClCH_2$—CO_2H	41, 42
Cl_2CH—CO_2H	43–45
Cl_3C—CO_2H	44, 46
F_3C—CO_2H	47–53, 55
$F(CF_2)_n$—CO_2H (n = 1, 2)	51, 53, 54
$HSCH_2CO_2H$	56
$HS(CH_2)_2CO_2H$	57
$HO(CR^1R^2)CO_2H$ (R^1, R^2 = H, alkyl, aryl)	58, 59
α-Amino acids	60–65
cyclohexyl-$(CH_2)_nCO_2H$ (n = 2, 3)	66
$HO_2C(CH_2)_2CO_2H$[a]	67
$PhSO_2NHCH(R)(CH_2)_nCO_2H$ (R = CO_2H, etc.)	68
$RSCH_2CO_2H$ (R = alkyl)	69
$ArOCH_2CO_2H$ (Ar = aryl)	70, 71
$RCH_2CH(NH_2)CO_2H$ (R = aryl, hetaryl, etc.)	72
(ferrocenyl)$(CH_2)_nCO_2H$ (n = 1–5)	73
$PhCH_2CO_2H$	18, 22, 27, 74–76
p-$IC_6H_4CO_2H$	77a
p-$H_2NO_2SC_6H_4(CH_2)_nCO_2H$ (n = 1, 2)	77b
$ArCH(OH)CO_2H$	78
(2-benzimidazolyl)$(CH_2)_2CO_2H$	79
(1- and 2-benzotriazolyl)CH_2CO_2H	80
(3-indolyl)CH_2CO_2H	81
(2-oxo-3-benzoxazolyl)$(CH_2)_nCO_2H$ (n = 1–3)	82
$(CH_3)_2C{=}CHCO_2H$	83
$CH_3C(Cl){=}CHCH_2CO_2H$	84
$CH_3C(Cl){=}CHCH_2CH_2CO_2H$	85–87
$ArCO_2H$ (Ar = aryl)	22, 23, 25, 27, 88–100
3-Fluoronaphthyl-2-CO_2H	101
3-($ArSO_2NH$)naphthyl-2-CO_2H	100
R-CO_2H (R = 5-membered ring containing N and S)	102, 103
 [X = CH_2, $(CH_2)_2$; R = H, alk, etc.]	104
R—CO_2H (R = 2-furyl, 2-pyridyl, etc.)	105
(2-pyridyl)-CO_2H	106
(4-pyridyl)-CO_2H	107
(2-quinolinyl)-CO_2H	108
(5-benzimidazolyl)carboxylic acid derivatives	109, 110

[a] The product is a carboxylalkylbenzimidazole.

[b] See text.

TABLE 1.2. SYNTHESIS OF BISBENZIMIDAZOLES BY THE REACTION OF *o*-ARYLENEDIAMINES[a] WITH DICARBOXYLIC ACIDS

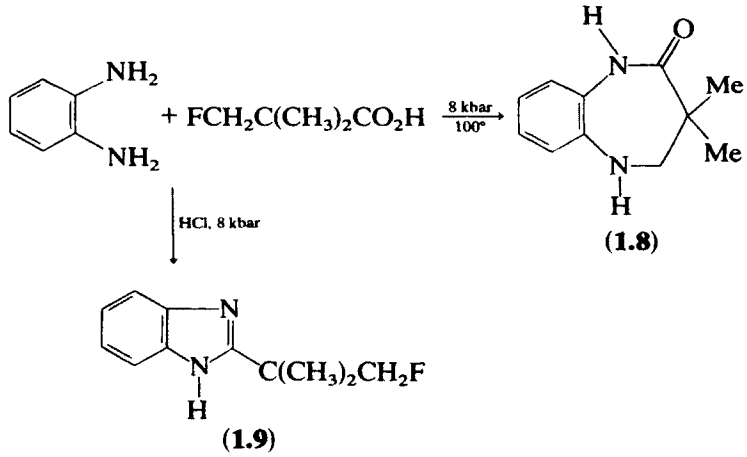
X in HO_2CXCO_2H	Ref.
$(CH_2)_2$	28, 111, 112
$(CH_2)_4$	113
CH=CH	114
$CH_2CH(OH)$	114
$[CH(OH)]_2$	115
$(CH_2)_8$	116
$(CF_2)_n$ (n = 1, 2)	117
$(CH_2)_n$ (n = 2, 4, 6, 8)	
$[CH(OH)]_2$	118
$(CH_2)_2S(CH_2)_2$	
$[CH(OH)]_4$	119
	120
$CH(OH)CH_2$	121
$(CH_2)_n$ (n = 2–4, 6)	
$[CH(OH)]_n$ (n = 2, 4)	
$CH(CH_3)CH_2$	122
$(CH_2)_2S(CH_2)_2$	
$CH(OH)CH_2$	
CH(OH)CH(R) (R = H, OH)	123
$(CH_2)_n$ (n = 1–8, 10)	124
$[(CH_2)_nCR_2(CH_2)_m]_2SO_2$ (n = 0, 1; m = 0–4; R = H, alk)	125
	126
 (in reactions with tetra amino derivatives)	127 (*cf.* 128, 129)

[a] The nature of substituents in these aryl rings is not indicated.

general the Phillips synthesis, in which the carboxylic acid is heated with the diamine in aqueous hydrochloric acid,[6] is used. This conventional procedure works satisfactorily for the preparation of most 2-alkyl derivatives but frequently fails or gives poor yields when applied to 2-aryl analogs. For example, the Phillips synthesis of 2-phenylbenzimidazole gives only a trace amount of the desired product,[130] and it is necessary to effect this transformation in a sealed tube at 180°.[131] Nevertheless, incorporation of either electron-withdrawing or -attracting groups into the aryl ring of the diamine results in only fair to poor yields of benzimidazole derivatives.[132] The discovery that polyphosphoric acid is an effective, convenient, and general catalyst for effecting such reactions is thus an important one.[94] Using this procedure, 2-arylbenzimidazoles are obtained in moderate to good yields (generally 50–85%) and high working pressures are not required. Alterna-

tive procedures for 2-aryl derivatives include the use of phosphorous pentoxide as a dehydrating agent[99] or azeotropic dehydration from kerosine[97] or xylene[99] solvent.

As mentioned earlier, most aliphatic carboxylic acids react normally in the Phillips process, but acids containing bulky substituents, such as adamantane 1-carboxylic acid[133] and 2,2-dimethylpropionic acid,[134,135] either do not react or give low yields of benzimidazoles. This poor reactivity has been attributed[134] to a combined effect of steric hindrance and a diminished electrophilic reactivity of the carboxyl group. Reactions in which ionic intermediates are formed from neutral reactants are normally accelerated in polar solvents at very high pressures,[136] and with this in mind Holan and coworkers[40] have been successful in converting hindered aliphatic acids into benzimidazoles at pressures of up to 8 kbar (1 kbar = 10^5 N $m^{-2} \equiv$ 986.1 atm); yields of 2-R-substituted derivatives are, for example, R = *t*-Bu (66%), CMe_2CH_2Cl (83%), and 1-adamantyl (48%). Reactions of the Phillips type probably[137] occur via intermediate *o*-aminoanilides, and while these were not isolated in the high-pressure reactions[40] it is interesting to note the formation of 1,3,4,5-tetrahydro-3,3-dimethyl-1,5-benzodiazepin-2-one (**1.8**) from the reaction of *o*-phenylenediamine with 3-fluoro-2,2-dimethylpropionic acid. When the reaction is carried out in the presence of an equivalent amount of hydrochloric acid, the appropriate benzimidazole derivative (**1.9**) is formed, but this is not converted into the benzodiazepinone (**1.8**) under the original conditions. Evidently the strong acid suppresses nucleophilic displacement of fluoride and favors benzimidazole formation.



(**1.8**)

(**1.9**)

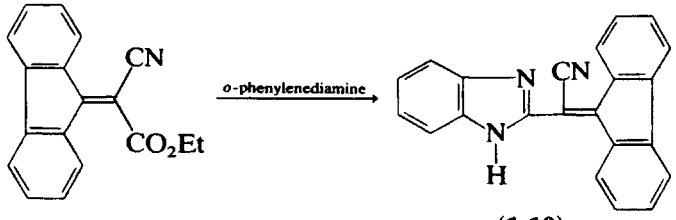
An additional modification to the original procudure is the use of formic acid in the presence of a mixture of hydrochloric acid and an acid resin [Dowex-50W-X8 (strong sulfonic acid)];[138] the reactions are carried out at room temperature, hence operating conditions are somewhat milder than in

the normal Phillips method (4 *M* HCl under reflux). An example of the utility of this method is the high-yield (96%) synthesis of the 5-R derivative (R = CH=CHCO$_2$H), which cannot be synthesized by the Phillips method.[138] The technique has been used to synthesize other benzimidazole-5-R derivatives (R = CO$_2$H, 62%; Cl, 30%; Me, 30%)[139] and 5,5'-bisbenzimidazole (75%), but the scope of the reaction in the context of synthesis of a variety of 2-substituted benzimidazoles has not been evaluated.

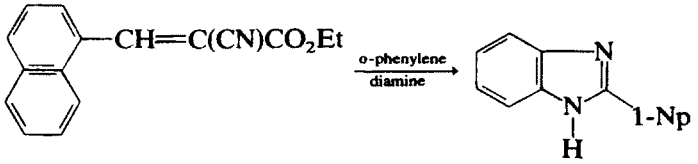
Carboxylic Acid Derivatives (Esters, Amides, Anhydrides, and Chlorides)

Routine procedures involving the condensation of *o*-arylenediamines and carboxylic acid derivatives are listed in Table 1.3.[140–170] A recent variant of the conventional procedure using esters is the method using thioesters.[154] In a typical reaction the diamine is treated with the thioester in aqueous ethanol at room temperature with the pH adjusted to ~8; hydrogen sulfide is aspirated, and the reaction is monitored by disappearance of the red color of the thioester. Yields are ~90%, and the method has been used for the synthesis of 2-carbamic acid ester derivatives.[155]

The reaction of *o*-phenylenediamine with fluoren-9-ylidenecyanoacetic ester (see Table 1.3) proceeds normally to give the desired benzimidazole (**1.10**), but 1-naphthylidene analogs give rise to 1-naphthylbenzimidazole (**1.11**) in good yield.[149] The 1-naphthyl analog of (**1.10**) is easily accessible, however, by allowing 1-cyanomethylbenzimidazole to react with 1-naphthaldehyde.[149]



(1.10)



(1.11)

(1-Np = 1-naphthyl)

TABLE 1.3. SYNTHESIS OF BENZIMIDAZOLES BY THE REACTION OF *o*-ARYLENEDIAMINES WITH CARBOXYLIC ACID ESTERS, AMIDES, ANHYDRIDES, AND CHLORIDES

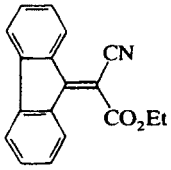
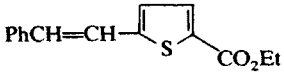
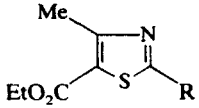
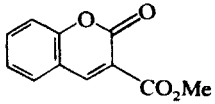
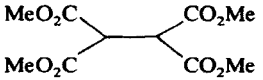
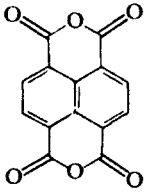
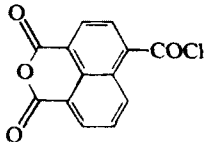
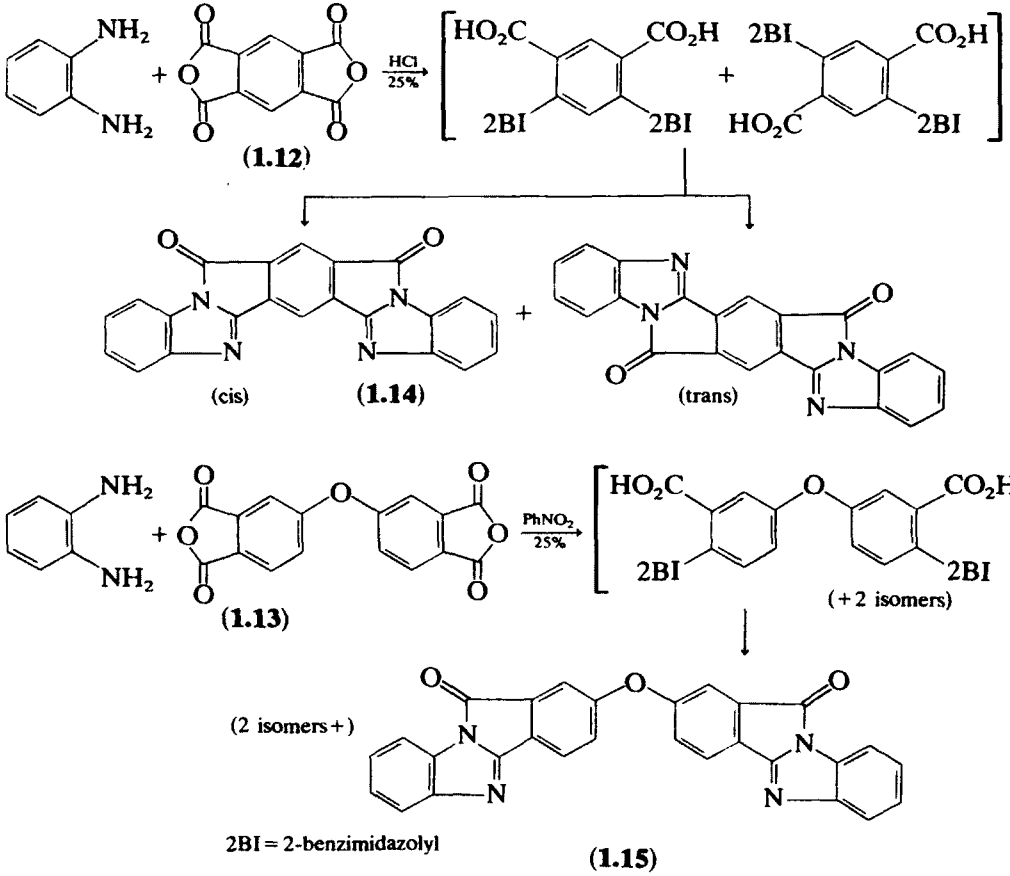
Carboxylic acid derivative	Ref.
$H_2NCH_2CO_2Et$	140
$NCCH_2CO_2Et$	141–143
$NCCH(R)CO_2Et$ (R = alkyl)	144
$CF_3(CF_2)_2CO_2Ph$	145
$BrCH_2COCO_2Et$	146, 147
$PhCO_2Ph$	148
	149[a]
$ArCH(CN)CO_2Et$ (Ar = aryl)	150
	151
 (R = halogen, NH-alkyl)	152
	153
$R—CS_2R^1$ (R = Ph, Me; R^1 = Et, CH_2CO_2H)	154[a]
RO_2CNHCS_2R (R = alkyl)	155[a]
$EtO_2CCH_2CO_2Et$ 	156
$RCONHCH(R)CONH_2$ (R = alkyl or aryl)	157
$H_2NCO(CH_2)_nCONH_2$ (n = 0, 2)	158
$RNHCO(CH_2)_nCONHR$ (n = 0, 4, 8, R = $HOCH_2CH_2$)	
$NCCH_2CONH_2$	159
$PhCONH_2$	160
$(CH_3CO)_2O$	161–163
pyromellitic anhydride	164, 165[a]
	166

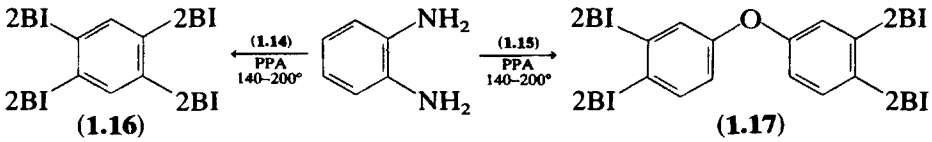
TABLE 1.3. (*Continued*)

Carboxylic acid derivative	Ref.
CH_3COCl	167, 168
o-ClC_6H_4COCl	169
	170

[a] See text.

Reactions[164,165] of pyromellitic anhydride (**1.12**) and the analogous ether (**1.13**) with *o*-phenylenediamine are of interest as model studies of the synthesis and properties of polybenzimidazoles.[171] In this manner substrates (**1.14, 1.15**) for the synthesis of complex model compounds (**1.16, 1.17**) have been prepared, although it may be noted that the isomer distributions in mixtures of (**1.14**) and (**1.15**) have not been determined.





2BI = 2-benzimidazolyl
PPA = polyphosphoric acid

Imino Ethers (Imidates)

Examples of the synthesis of benzimidazoles from reactions of *o*-arylenediamines with imino ethers (imidates) are summarized in Table 1.4.[172–199] The scope of the imidate[200] procedure was assessed in early work by Acheson and King.[201] One problem concerning the Phillips reaction is that the diamine often competes successfully for the proton of the acid catalyst, hence inhibiting nucleophilic addition to the carbonyl group; this difficulty is surmounted by replacing the carbonyl group by the more basic imino group, and very often the imidate method is superior to the conventional Phillips approach. For example, Phillips reaction of *o*-phenylenediamine with 2,4-dinitrophenylacetic acid takes place only under drastic conditions, and considerable resinification occurs;[188] conversely, reaction of the diamine with the hydrochloride of ethyl 2,4-dinitrophenylacetimidate under reflux gives the desired 2-(2,4-dinitrobenzyl)-benzimidazole in 84% yield.[188]

The synthesis of 2-(trichloromethyl)benzimidazole presents similar difficulties by the Phillips approach: a complex mixture is obtained from the reaction of *o*-phenylenediamine and trichloroacetic acid, from which 2,2′-bibenzimidazolyl (**1.18**) and the anilide (**1.19**) are isolated.[202] Since these

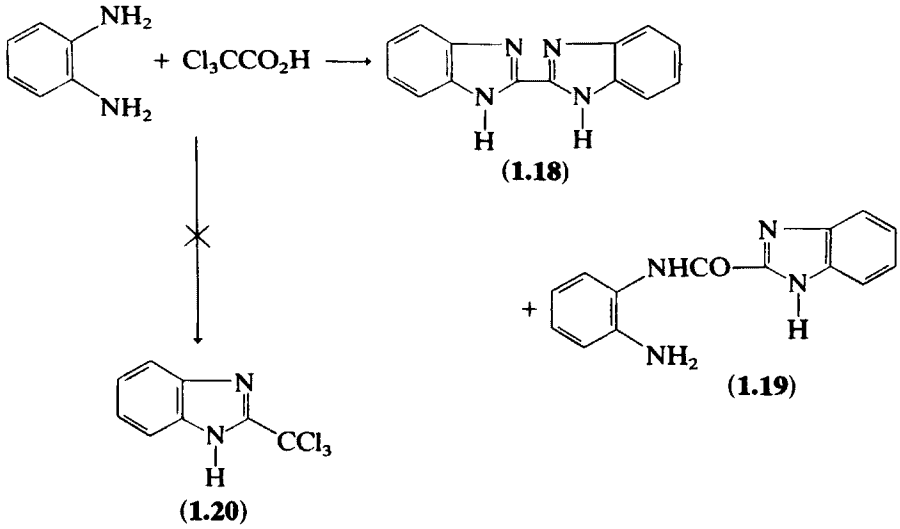
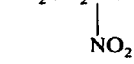
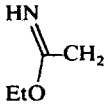
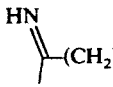
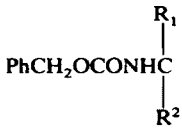
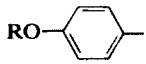
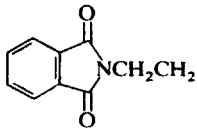
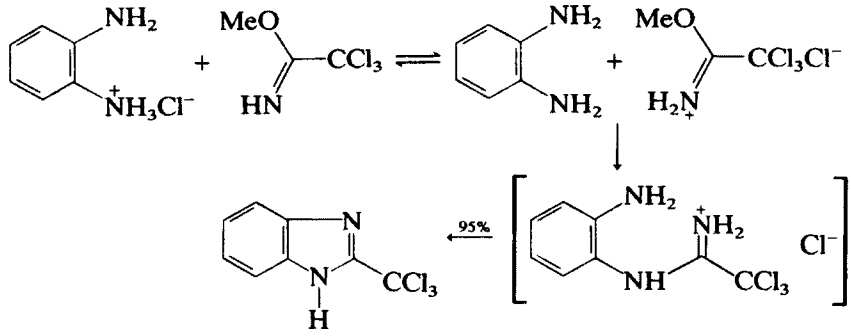


TABLE 1.4. SYNTHESIS OF BENZIMIDAZOLES BY THE REACTION OF *o*-ARYLENE-DIAMINES WITH IMINO ETHERS (IMIDATES)

Substituent (R^1) in the imino ether:  OR^2 (R^2 = Me or Et)	Ref.
CCl_3	172–175
H, alkyl, hydroxylalkyl, etc.	176
H, alkyl, aralkyl, etc.	177
Polyhaloalkyl, alkenyl, alkyl-S-	178
	179
$(CH_2)_2C(NO_2)_2R$ (R = NO_2, $CH_2CH_2CO_2Me$)	180
CH_2CO_2Et	181, 182
CH_2CN	182
$(CH_2)_nBr$ (n = 3–5)	183
$CH_2CH_2NR^1R^2$ (NR^1R^2 = piperidino, etc.)	184
	185
 (n = 4, 8)	186
$ArCH_2$ (Ar = aryl)	187–189
$ArNHCH_2$	190
 (R^1, R^2 = H or alkyl)	191
 (R = H, alkyl)	192
$ArNHCH_2CH_2$	193
	194
2-Furyl	195
CH_2CH_2-2-benzimidazolyl	196
$(CH_2)_2PO(OR)_2$ (R = alkyl)	197
$(CH_2)_2OP(OR)Me$ (R = alkyl)	198
$(CH_2)_2C(NO_2)_2(CH_2)_2C(OEt)=NH$	199

two products (**1.18** and **1.19**) are also formed by the reaction of 2-trichloromethylbenzimidazole (**1.20**) with *o*-phenylenediamine, the former is evidently an intermediate. Reaction of the appropriate imidate ester with *o*-phenylenediamine or its disalt gives the bibenzimidazolyl (**1.18**) in 90% yield, and indeed this is the synthetic method of choice for this compound and substituted analogs. However, by using *o*-phenylenediamine monosalt as such, or by generating it *in situ*, the reaction with methyl trichloroacetimidate gives 95% of the 2-trichloro derivative (**1.20**) even at room temperature.[202] Suppression of the reaction giving rise to 2,2'-bibenzimidazolyl (**1.18**) requires a rapid and complete initial reaction of the diamine with the imidate to give an intermediate (**1.21**), and this can be achieved at intermediate acidities (pH ~ 4).



(1.20) **(1.21)**

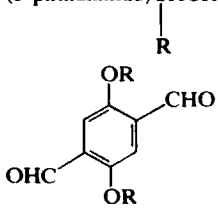
Aldehydes

A summary of procedures leading to 2-substituted benzimidazoles by the reaction of *o*-arylenediamines with aldehydes is presented in Table 1.5.[203-225] In this method, the reactants are condensed in the presence of an oxidant[1,6] such as cupric acetate (Weidenhagen procedure),[226] mercuric oxide (for 2-$NHCO_2Me$)[204] or chloranil (for 2-furyl).[219b]

An improvement on the conventional method is the use of the sodium bisulfite addition adduct of the aldehyde.[227] The reactions are carried out in boiling ethanol, yields are good [e.g., 2-Ph (90%); 2(3-pyridyl) (97%)], and there is little risk of decomposition of labile substituents. Evidently, the aldehyde route is suitable for the preparation of 2-hetaryl derivatives, and improved yields are also obtained by using the bisulfite addition complex of the aldehyde (for 2-furyl derivatives).[219c]

The superficially simple reaction of *o*-phenylenediamine and its derivatives with benzaldehyde has been studied in detail.[210] Benzaldehyde and *o*-phenylenediamine react rapidly at −20° to produce the imine (**1.21A**), and when the mixture is warmed to room temperature, 2-phenylbenzimidazole

TABLE 1.5. SYNTHESIS OF BENZIMIDAZOLES BY THE REACTION OF *o*-ARYLENEDIAMINES WITH ALDEHYDES

Aldehyde[a]	Ref.
RCHO (R = alkyl, aryl, aralkyl, hetaryl)	203
$MeO_2CNHCHO$	204
CH_2O[b]	205
ArCHO (Ar = aryl)	206–214
2-Furyl-CHO	215–219
(2-Furyl)CH=CHCHO	220
(3-thienyl)CHO	221
(2-pyridyl)CHO	222
(1-isoquinolinyl)CHO (2-quinolinyl)CHO	223
(3-pyridyl)CHO (3-quinolinyl)CHO	219a
(3-phthalimido)CHCHO (R = H, alkyl)	224
	225

[a] Substituents in the aldehyde and diamine are not shown.
[b] The products are 1-methylbenzimidazoles.

(**1.22**) is formed in 19% yield together with a molecular complex of (**1.23**) and (**1.24**). 2-Phenylbenzimidazole (**1.22**) must arise by oxidation of precursors (**1.21** or **1.25**), and it is suggested that the compensating reduction is that of the imine (**1.21**) to the diamine (**1.26**).[210] In support of this it has been shown that (**1.26**) reacts rapidly with benzaldehyde to give the dihydro compound (**1.24**), as the molecular complex with (**1.23**), together with 1,3-dibenzyl-2-phenylbenzimidazoline (**1.27**); NMR evidence has been adduced for the intermediacy of an imine in this reaction, and an oxidation–reduction step similar to (**1.21** → **1.26**) presumably occurs. A brief study of substituent effects has been carried out.[214] 3-Methyl-*o*-phenylenediamine reacts with benzaldehyde in acetic acid to give 2-phenyl-4-methylbenzimidazole (**1.28**) and the 1-benzyl derivative (**1.29**) but not the isomer (**1.30**).

The reaction of *o*-arylenediamines with formaldehyde gives rise to 1-methylbenzimidazoles,[228,229] and this type of process has been studied in detail.[205] It is possible to use the more easily accessible *N*-monoacetyl *o*-phenylenediamine derivatives, and in this manner a variety of 1-methyl derivatives can be prepared in yields of 42 to 59%.[205]