QUINAZOLINES

Supplement I

D. J. Brown

Research School of Chemistry
Australian National University
Canberra

AN INTERSCIENCE® PUBLICATION

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Supplement I

This is the fifty-fifth volume in the series

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

THE CHEMISTRY OF HETEROCYCLIC COMPOUNDS

A SERIES OF MONOGRAPHS

EDWARD C. TAYLOR, *Editor*

ARNOLD WEISSBERGER, *Founding Editor*

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Dedicated to
the Memory of

Arnold Weissberger
1899–1984

Zichrono livracha

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The Chemistry of Heterocyclic Compounds
Introduction to the Series

The chemistry of heterocyclic compounds is one of the most complex and intriguing branches of organic chemistry, of equal interest for its theoretical implications, for the diversity of its synthetic procedures, and for the physiological and industrial significance of heterocycles.

The Chemistry of Heterocyclic Compounds, published since 1950 under the initial editorship of Arnold Weissberger, and later, until Dr. Weissberger's death in 1984, under our joint editorship, has attempted to make the extraordinarily complex and diverse field of heterocyclic chemistry as organized and readily accessible as possible. Each volume has traditionally dealt with syntheses, reactions, properties, structure, physical chemistry, and utility of compounds belonging to a specific ring system or class (e.g., pyridines, thiophenes, pyrimidines, three-membered ring systems). This series has become the basic reference collection for information on heterocyclic compounds.

Many broader aspects of heterocyclic chemistry are recognized as disciplines of general significance that impinge on almost all aspects of modern organic chemistry, medicinal chemistry, and biochemistry, and for this reason we initiated several years ago a parallel series entitled General Heterocyclic Chemistry, which treated such topics as nuclear magnetic resonance, mass spectra, and photochemistry of heterocyclic compounds, the utility of heterocycles in organic synthesis, and the synthesis of heterocycles by means of 1,3-dipolar cycloaddition reactions. These volumes were intended to be of interest to all organic, medicinal, and biochemically-oriented chemists, as well as to those whose particular concern is heterocyclic chemistry. It has, however, become increasingly clear that the above distinction between the two series was unnecessary and somewhat confusing, and we have therefore elected to discontinue *General Heterocyclic Chemistry* and to publish all forthcoming volumes in this general area in *The Chemistry of Heterocyclic Compounds* series.

This series, together with the international community of chemists concerned with heterocyclic chemistry, is indebted once again to the indefatigable efforts of Dr. D. J. Brown. His record of authoring classics in nitrogen heterocyclic chemistry (*The Pyrimidines*, *The Pyrimidines Supplement I*, *The Pyrimidines Supplement II*, *Pteridines*) is now extended by the publication of an exhaustive supplement to Wilf Armarego's initial volume on *Quinazolines*. We extend once again our congratulations and our thanks to Dr. Brown for a further outstanding contribution to the literature of heterocyclic chemistry.

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Princeton, New Jersey

EDWARD C. TAYLOR

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Preface

Dr. Wilf Armarego's original volume, *Quinazolines*, appeared within this series in 1967. Not only did it represent an excellent summary of quinazoline chemistry to the end of 1965, but it clearly facilitated and stimulated considerable subsequent research in the field. Thus the need for a supplementary volume covering the last 30 years' literature has become pressing. On account of a radical change in his research interests during that period, Dr. Armarego felt disinclined to undertake such an updating task, which consequently fell to the present author, whose interests have remained broadly within this area.

Because of a great expansion in the scope of quinazoline chemistry and for other pragmatic reasons, it has been necessary to inaugurate a massive chapter on primary syntheses and to reorganize completely the content of remaining chapters so that they might better reflect and emphasize current research trends. However, the status of the present volume as a *supplement* has been maintained by sectional cross-references (e.g., *H* 42) to pages of the original volume (*Hauptwerk*) where earlier relevant information may be found. Moreover, in view of the vast increase in the number and types of individual quinazolines described in recent literature, it has been necessary to abandon the myriad classified tables of known quinazolines in favor of a single alphabetical table of simple quinazolines. To facilitate recovery of any earlier data from tables in the original volume, a cross-reference (e.g., *H* 151) has been added (when appropriate) to each individual entry in the new table. The opportunity has been taken to bring the chemical nomenclature into line with current IUPAC recommendations [*Nomenclature of Organic Chemistry, Sections A–F, H* (Eds. J. Rigaudy and S. P. Klesney, Pergamon Press, Oxford, 1970)] with one important exception: in order to keep "quinazoline" as the principal part of each name, those groups that would normally qualify as principal suffixes, but that are not attached directly to the nucleus, are rendered as prefixes. For example, 2-carboxymethyl-4(3*H*)-quinazolinone is used instead of α-(4-oxo-3,4-dihydro-2-quinazolinyl)acetic acid. Secondary or tertiary amino groups are rendered invariably as prefixes. Trivial names, still occasionally used for some naturally occurring oxyquinazolines, are included as appropriate in the table of simple quinazolines and/or in Section 4.8.4. Finally, to avoid repetition and inevitable confusion, literature references are presented as a single list rather than as smaller lists at the end of each chapter.

In preparing this *supplement*, the massive patent literature has been ignored in the belief that useful factual material therein has appeared subsequently in the regular literature. It must be mentioned also that a small but significant proportion of the research papers quoted as references have proved very disappointing in terms of essential detail, thereby reflecting badly on their authors and on the editorial policies of the journals in which they appeared. The

popularity of quinazoline research in India and Egypt is both noteworthy and rather puzzling.

Although the original papers on quinazoline chemistry during the last 30 years came from no less than 55 countries, they appeared in only 16 languages (ignoring any subsequent translations): from the following percentages, it is evident that the laudable trend toward publication of research results in a widely understood major language has continued.

English	75.9%
German	11.0%
Russian	5.9%
French	2.3%
Japanese	1.4%
Italian	1.1%
Romanian	0.6%
Polish	0.4%
Ukrainian	0.4%
Spanish	0.2%
Bulgarian	0.2%
Chinese	0.2%
Hungarian	0.1%
Czech	0.1%
Korean	0.1%
Portugese	<0.1%
Slovenian	<0.1%

I am greatly indebted to my former colleagues, Drs W. L. F. Armarego and G. B. Barlin, for invaluable discussions; to successive Deans of the Research School of Chemistry (Professors A. L. G. Beckwith, L. N. Mander, and J. W. White) for the provision of excellent postretirement accommodation and facilities within the School; to Dr. Adam Vincze (Israel Institute for Biological Research) for kind advice; to the branch librarian, Mrs J. Smith, for unfailing cooperation; and to my wife, Jan, for her cheerful forebearance and unstinting assistance during indexing, proofreading, and the like.

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DES J. BROWN

Contents

CHAPTER 1

Primary Syntheses

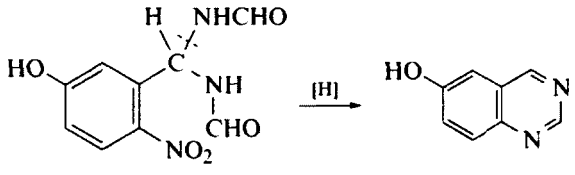
The primary synthesis of quinazolines may be accomplished by cyclization of benzene substrates already bearing appropriate substituents; by treatment of benzene substrates with synthons to provide one or more of the ring atoms required to complete the pyrimidine ring; by analogous processing of preformed pyrimidine substrates; by elaboration from several acyclic synthons; or by rearrangement, ring expansion/contraction, degradation, or modification of appropriate derivatives of other heterocyclic systems. Partially or even fully reduced quinazolines may often be made by rather similar procedures; such cases are usually illustrated toward the end of each subsection. Examples of any pre-1966 syntheses in each category may be found from the cross-references (e.g., *H* 48) to Armarego's parent volume;[2414] some post-1966 material has been reviewed elsewhere in brief.[409,2382,2383]

1.1. FROM A SINGLE BENZENE SUBSTRATE

A remarkable number of quinazoline syntheses have been carried out by preforming appropriate benzene derivatives for cyclization to required quinazolines by the formation of one remaining bond on the pyrimidine side of the molecule.

1.1.1. By Formation of the 1,2-Bond (*H* 11,48,394)

Such a process is typified by the facile conversion of 3-hydroxy-6- nitrobenzaldehyde into 3-(diformamido)methyl-4-nitrophenol (**1**) with subsequent reductive cyclization (Zn/AcOH) to 6-quinazolinol (**2**) (57%),[2359] representing a classic example of Reidel's synthesis (*H* 48). Rather similar reductive procedures gave 5,6,8-trimethoxy-7-methylquinazoline (48%),[2363] 5,8-dimethoxyquinazoline

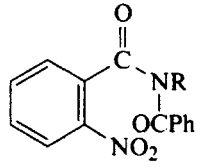


(1) (2)

(41% or 93%),[585,1604] and 5,8-dibutoxyquinazoline (79%).[595] Other reductive processes and several completely different ways to achieve cyclization by 1,2-bond formation are illustrated in the following examples.

Reductive cyclizations

N-Acetyl-2-nitrobenzamide (**3**, R = H) gave 2-methyl-4(3*H*)-quinazolinone 1-oxide or 2-methyl-4(3*H*)-quinazolinone (electrolytic: according to conditions).[2399]

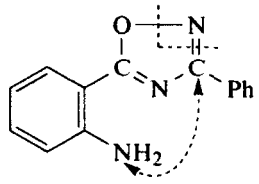


(3)

N-Acetyl-*N*-methyl-2-nitrobenzamide (3, R = Me) gave 2,3-dimethyl-4(3*H*)-quinazolinone [CO, $Ru_2(CO)_{12}$, dioxane, 10 atm, 140°, 16 h: 93%].[2406]

N-Ethoxycarbonyl-*N*-methyl-2-nitrobenzamide gave 1-hydroxy-3-methyl-2,4(1*H*,3*H*)-quinazolinedione ($NaBH_4$, NaOH, H_2O, 20°, 90 min: 24%).[425]

5-*o*-Aminophenyl-3-phenyl-1,2,4-oxadiazole (**4**) gave 2-phenyl-4(3*H*)-quinazolinone (H_2, Pd/C, EtOH, 1 atm, 20°: 72%).[991]

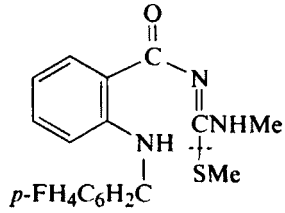


(4)

Also other examples.[1766,2067]

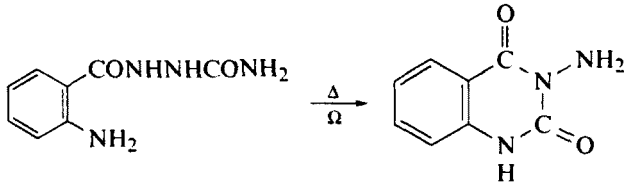
Thermal cyclizations

2-*p*-Fluorobenzylamino-*N*-(α-methylamino-α-methylthiomethylene)benzamide (**5**) gave 1-*p*-fluorobenzyl-2-methylamino-4(3*H*)-quinaolinone [$(MeOCH_2CH_2)_2O$, trace NaOH, reflux, 2 h: 74%].[906]



(5)

o-(Semicarbazidocarbonyl)aniline (**6**) gave 3-amino-2,4(1*H*,3*H*)-quinazolinedione (**7**) (decalin, reflux, 2 h: 50%; involving a rearrangement step).[485]

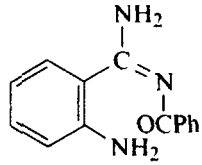


(**6**) (**7**)

Also other examples.[2554]

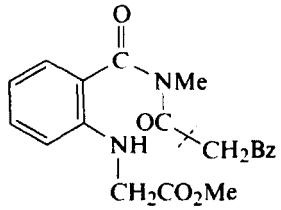
Cyclizations in acid

o-Amino-*N*-benzoylbenzamidine (**8**) gave 2-phenyl-4-quinazolinamine (<0.1M HCl, 20°, 1 min: 95%).[1232]



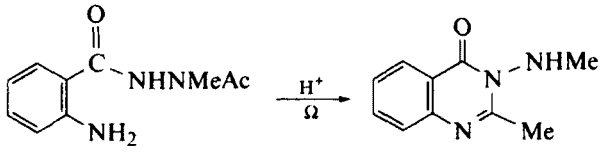
(**8**)

o-(Methoxycarbonylmethyl)amino-*N*-methyl-*N*-(phenacylcarbonyl)benzamide (**9**) gave 1-methoxycarbonylmethyl-3-methyl-2,4(1*H*,3*H*)-quinazolinedione (10% AcOH/EtOH, reflux, 2 h: 42%).[2270]



(**9**)

N'-Acetyl-*o*-amino-*N'*-methylbenzohydrazide (**10**) gave 2-methy-3-methylamino-4(3*H*)-quinazolinone (**11**) (10% H_2SO_4, 80°, 30 min: 78%; involves rearrangement).[921]



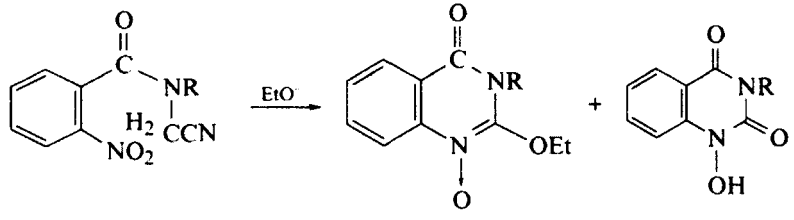
(**10**) (**11**)

Also other examples.[773,2400]

Cyclizations in base

N-Cyanomethyl-*o*-nitrobenzamide (**12**, R = H) gave 2-ethoxy-4(3*H*)-quinazolinone 1-oxide (**13**, R = H)(EtONa, EtOH, reflux, 1 h: ~ 35%; involves CN replacement) and some 1-hydroxy-2,4(1*H*,3*H*)-quinazolinedione (**14**, R = H) (from the aqueous mother liquors).[182]

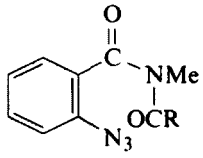
In contrast, *N*-cyanomethyl-*N*-methyl-*o*-nitrobenzamide (**12**, R = Me) gave only 1-hydroxy-3-methyl-2,4(1*H*,3*H*)-quinazolinedione (**14**, R = Me) (EtONa, EtOH, reflux, 1 h, aqueous workup: 93%; or $NaOH/H_2O$, reflux, 30 min: ~ 90%).[187]



(**12**) (**13**) (**14**)

Wittig-assisted cyclizations

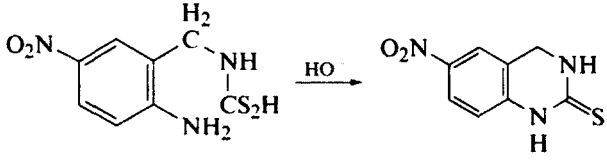
N-Acetyl-2-azido-*N*-methylbenzamide (**15**, R = Me) gave 2,3-dimethyl-4(3*H*)-quinazolinone (Ph_3P, xylene, 20°, 2 h: > 95%); likewise, 2-azido-*N*-cinnamoyl-*N*-methylbenzamide (**15**, R = CH:CHPh) gave 3-methyl-2-styryl-4(3*H*)-quinazolinone (> 95%).[2079,2131]



(**15**)

Cyclizations to hydroquinazolines

2-(Dithiocarboxy)aminomethyl-4-nitroaniline (**16**) gave 6-nitro-3,4-dihydro-2(1*H*)-quinazolinethione (**17**) (0.1M NaOH, 85°, 3 h: ~ 50%).[374]

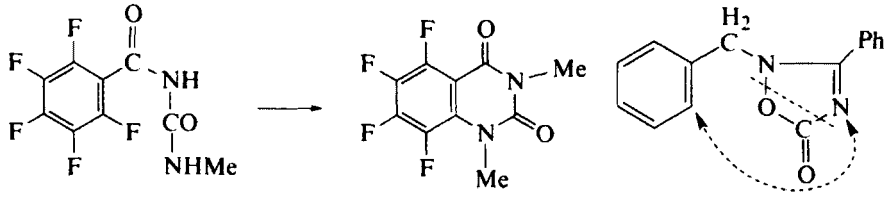


(**16**) (**17**)

Also other examples.[430,1811,1890]

1.1.2. By Formation of the 1,8a-Bond

This unappealing route has been used to make a few aromatic and reduced quinazolines. Thus treatment of *N*,*N*′-dimethyl-*N*-pentafluorobenzoylurea (**18**) with potassium fluoride in refluxing dimethylformamide for 7 h gave 5,6,7,8-tetrafluoro-1,3-dimethyl-2,4(1*H*,3*H*)-quinazolinedione (**19**, R = F) (49%) but, when sodium hydride was used in place of potassium fluoride, the only product was the 7-dimethylamino derivative (**19**, R = NMe_2) (66%);[1317] prolonged irradiation of 2-benzyl-3-phenyl-1,2,4-oxadiazol-5(2*H*)-one (**20**) gave a little 2-phenylquinazoline;[225] 2-ureidomethylenecyclohexanone (**21**) in boiling dilute alkali gave 5,6,7,8-tetrahydro-2(1*H*)-quinazolinone (**22**) (92%);[190] and other examples have been described.[423,1692,2046]



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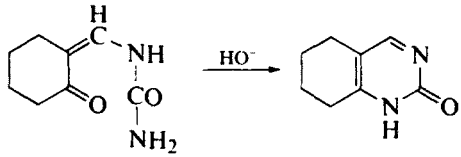


(21) (22)

1.1.3. By Formation of the 2,3-Bond

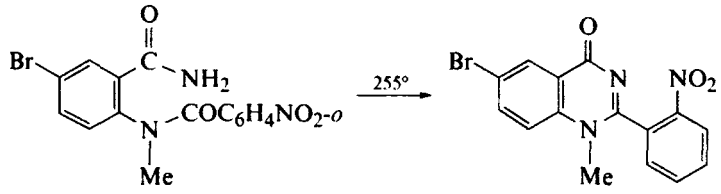
This route has been used widely to prepare quinazolines (and a few hydroquinazolines) from a variety of substrate types, as described in the following subsections.

1.1.3.1. From *o*-Acylaminobenzamides (*H* 77,101)

The cyclization of *o*-acylaminobenzamides, usually to 4-quinazolinones, has been done in several ways as indicated in the following examples.

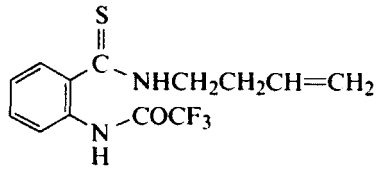
Thermal cyclizations

3-Bromo-6-(*N*-methyl-*o*-nitrobenzamido)benzamide (**23**) gave 6-bromo-1-methyl-2-*o*-nitrophenyl-4(1*H*)-quinazolinone (**24**) (neat, 255°, 30 min: 59%).[45]



(23) (24)

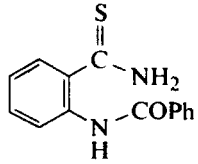
N-(But-3-enyl)-*o*-(trifluoroacetamido)benzamide (**25**) gave 3-but-3′-enyl-2-trifluoromethyl-4(3*H*)-quinazolinone (neat, 200°, 1 h: 85%).[1727]



(25)

o-(Pentafluoropropionamido)benzamide gave 2-pentafluoroethyl-4(3*H*)-quinazolinone (Me_2NCHO, reflux, 3 h: 76%).[914]

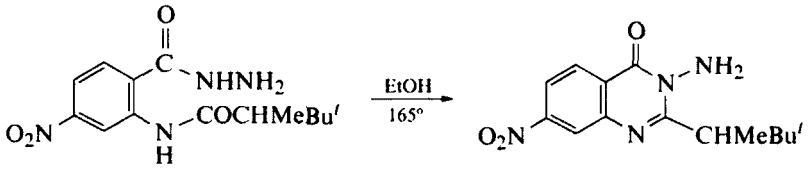
o-Benzamido(thiobenzamide) (**26**) gave 4-ethylthio-2-phenylquinazoline (Et_3OBF_4, CH_2Cl_2, reflux, 1 h: 82%; note the *S*-ethylation).[1060]



(26)

o-Cinnamamido-*N*-methylbenzamide gave 3-methyl-2-styryl-4(3*H*)-quinazolinone (neat, > 200°, 20 min).[537]

4-Nitro-2-(2,3,3-trimethylbutyramido)benzohydrazide (**27**) gave 3-amino-7-nitro-2-α,β,β-trimethylpropyl-4(3*H*)-quinazolinone (**28**) (EtOH, 165°, sealed, 12 h: 51%).[1954]

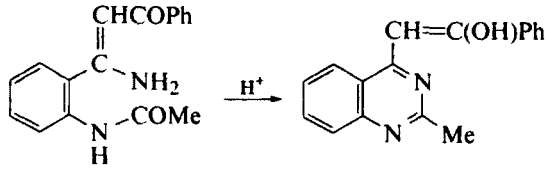


(27) (28)

Also other examples.[519,960,968,983,992,1197,1311,1345,1371,1391,1535,2116,2287]

Cyclizations in acid

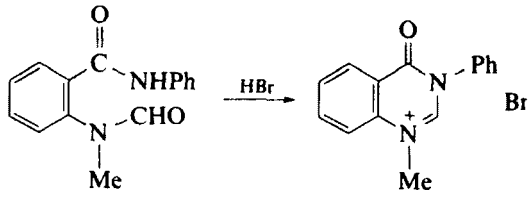
1-Acetamido-2-(α-amino-β-benzoylvinyl)benzene (**29**) gave 4-β-hydroxystyryl-2-methylquinazoline (**30**) (HCl, EtOH–H_2O, reflux, 30 min: ~75%).[1781]



(**29**) (**30**)

o-Chloroacetamido-*N*-(*o*-tolyl)benzamide gave 2-chloromethyl-3-*o*-tolyl-4(3*H*)-quinazolinone (AcOH, reflux).[2304]

o-(*N*-Methylformamido)benzanilide (**31**) gave 3-phenyl-4(3*H*)-quinazolinone 1-methobromide (**32**) (HBr, EtOH–H_2O, 20°, briefly: 84%).[352]

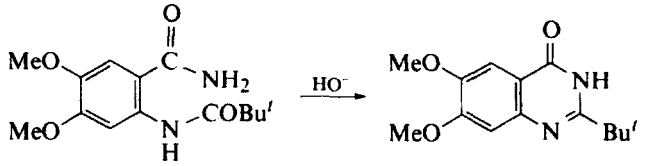


(**31**) (**32**)

Also other examples.[687,1033,1526]

Cyclizations in base

3,4-Dimethoxy-6-pivalamidobenzamide (**33**) gave 2-*t*-butyl-6,7-dimethoxy-4(3*H*)-quinazolinone (**34**) (1M NaOH, 70°, 5 min: 85%).[1354]

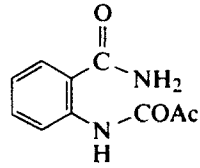


(**33**) (**34**)

o-(*o*-Azidobenzamido)benzamide gave 2-(*o*-azidophenyl)-4(3*H*)-quinazolinone (1.2M NaOH, 95°, 1 h: 85%).[1277]

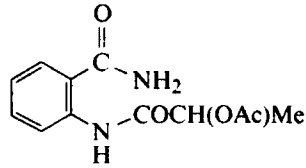
o-Pyruvamidobenzamide (**35**) gave 2-acetyl-4(3*H*)-quinazolinone (2M NaOH, reflux, 2 h: 60%).[185]

2,5-Dimethoxy-6-(phenoxyacetamido)benzamide gave 5,8-dimethoxy-2-phenoxymethyl-4(3*H*)-quinazolinone (NaOH, EtOH–H_2O, reflux, 24 h: 88%).[1999]



(35)

o-(2-Acetoxypropionamido)benzamide (**36**) gave 2-α-hydroxyethyl-4(3*H*)-quinazolinone (K_2CO_3, H_2O, 20°, 3 days: 75%; note the deacetylation).[2069]



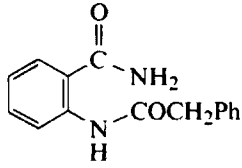
(36)

2-Acetamido-3,5-dibromo-*N*-methylbenzamide gave 6,8-dibromo-2,3-dimethyl-4(3*H*)-quinazolinone (EtOH, base, 20°, 2 days; $EtNH_2$ or Et_2NH: > 95%; Et_3N: 30%).[2184]

Also other examples, some illustrating the formation of hydroquinazolines or the further use of organic bases.[17,181,411,482,513,557,584,1346,1639,1981,2081,2098,2430,2505] Mechanistic aspects have been studied.[2555]

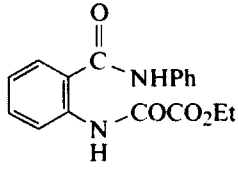
Cyclizations with dehydrating reagents

o-(2-Phenylacetamido)benzamide (**37**) gave 2-benzyl-4(3*H*)-quinazolinone (P_2O_5, xylene, reflux, 4 h: 54%).[1306]



(37)

o-(Ethoxalylamino)benzanilide (**38**) gave ethyl 4-oxo-3-phenyl-3,4-dihydro-2-quinazolinecarboxylate (PCl_3, PhMe, reflux, 1 h: 75%).[781]



(38)