Vakhid A. Mamedov

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Synthesis, Reactions, Mechanisms and Structure

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Foreword

Heterocycles form a fundamental basis for the development of pharmaceutical and agricultural products with wide applications. In this book the author describes the synthesis, and the chemical properties of an important class of heterocyclic chemistry, the quinoxalines.

Chapter 1 describes some properties of the Quinoxaline–As a Parent Heterocycle.

Chapter 2 covers recent advances in the Synthesis of Quinoxalines involving the methods based on the (a) condensation of 1,2-diaminobenzenes and derivatives with various two-carbon unit suppliers, (b) condensation of *o*-benzoquinone diimines and diimides with various two-carbon unit suppliers, (c) condensation of *N,N*-dimethyl(dibenzyl)ethylenediamine with 1,2- and 1,4-dihydroxybenzenes, (d) synthesis of quinoxalines from aniline and its derivatives, (e) synthesis of quinoxalines from heterocyclic systems and (f) synthesis of quinoxalines based on the carbocyclic system.

From the data presented in this chapter many original and interesting methods recently appeared for the synthesis of quinoxalines, which are difficult to obtain or in general are unobtainable. These new methods by Kaufmann, Tanimori, Kalinski and Shaabani are based on the reactions of a wide variety of compounds that deserve further attention.

Chapter 3 describes two methods of the Synthesis of Pyrrolo[l,2-*a*]quinoxalines based both on quinoxalines and pyrroles. Chapter 4 captures the Synthesis of Imidazo[1,5-*a*]- and Imidazo[1,2-*a*]quinoxalines. Chapter 5 discusses the Synthesis of Quinoxaline Macrocycles through (a) introduction of the quinoxaline system into macrocycles, (b) the closing of 1,n-bis(quinoxalin-1-yl)alkanes and (c) from both resorcin[4]arenes and quinoxalines. Chapter 6 demonstrates all known Rearrangements of Quinoxalin(on)es in the Synthesis of Benzimidazol(on)es and the interesting new rearrangements discovered by Mamedov, the author of this book, comprising (a) the acid catalysed conversion of "any of the spiro-derivatives of 1,2,3,4-tetrahydrtinquinoxalin-3-one with at least one mobile hydrogen atom in their spiro-forming component into benzimidazole derivative with the spiro-forming

component at position 2" and (b) the acid catalyzed rearrangement of "any of the spiro-derivatives of 1,2,3,4-tetrahydroquinoxalin-3-one without any mobile hydrogen atom in their spiro-forming component are on their way to the benzimidazolone derivative with the spiro-forming component at position 1".

Henk van der Plas

Preface

The book gives equal weight to each of the fundamental aspects of quinoxaline chemistry: synthesis, reactions, mechanisms, structure, properties, and uses. The first four chapters present a survey of the developments in quinoxaline chemistry since the publication of the monograph on "Condensed Pyrazines" by Cheeseman and Cookson in 1979. These chapters give a comprehensive coverage of the important quinoxaline-containing ring systems such as thiazolo[3,4-*a*]-, pyrrolo [1,2-*a*]-, imidazo[1,5-*a*]-, pyrano[2,3-*b*]quinoxalines, etc. Chapter five describes many new methods for the construction of quinoxaline macrocycles, which are important because of their application to optical devices and materials. The remaining sixth chapter gives a review of all the previously known rearrangements of heterocyclic systems that lead to benzimidazole derivatives. A critical analysis of these transformations reveals novel acid-catalyzed rearrangements of quinoxalinones giving 2-heteroaryl benzimidazoles and 1-heteroaryl benzimidazolones in the presence of nucleophilic reactants. The Appendix gives X-ray crystallographic data for a number of quinoxaline derivatives (41 samples) synthesized in the Laboratory of the Chemistry of Heterocyclic Compounds of the A.E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Scientific Centre of the Russian Academy of Sciences. The literature has been covered up to the end of 2013, with some additional data from publications in 2014 and 2015.

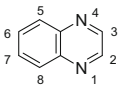
This book is the result of a collective effort. I find it necessary to acknowledge the assistance rendered by the compilers of this book Dr. Nataliya A. Zhukova, who contributed to the final version of the manuscript and also Dr. Elena A. Hafizova, Dr. Liliya V. Mustakimova and the authors of the dissertations Dr. A.A. Kalinin (in Chap. 6), Dr. D.F. Saifina (in Chap. 6), Ph.D. O.G. Isaykina (in Chap. 6), Ph.D. A. M. Murtazina (in Chap. 6) and Ph.D. V.R. Galimullina (in Chap. 6) as well as all my co-workers whose names appear in the references. My profound thanks are due to Ida H. Rapoport for her invaluable assistance in reading the first English version of the manuscript. Special acknowledgments are due to Prof. Aidar T. Gubaidullin for X-ray structural analyses of all the compounds and the X-ray structural analyses data in the Appendix. I take this opportunity to express my special thanks to the

administration and mainly to the director of the A.E. Arbuzov Institute of Organic and Physical Chemistry of the Kazan Research Center of the Russian Academy of Sciences Prof. Oleg G. Sinyashin for his interest in our research and to the Russian Foundation for Basic Research for funding (Grants No. 07-03-00613-a, 10-03-00413-a, 13-03-00123-a). The completion of this endeavor would have never been possible without the consent of Prof. Bert U.W. Maes from the University of Antwerp, whom I am extremely grateful to. And last, but no means least, I consider myself indebted to Profs. Yakov A. Levin and Ildus A. Nuretdinov of the A.E. Arbuzov Institute, Eugene A. Berdnikov of the Kazan University and Sadao Tsuboi of the Okayama University (Japan). Their dedication and skill taught me how to teach. I thank them.

Finally, I should like to thank Prof. John A. Joule from the University of Manchester, who has constantly provided me with helpful advice and criticism as regards the grammatical and editing aspects while the manuscript was in preparation. I am particularly grateful to my wife Dr. Vera L. Mamedova and my son Javid and daughter Sevil. They endured with patience and understanding the many days and nights of my staying at the Institute and the endless hours on the computer. They helped me in so many ways that are too numerous to mention.

Contents

Chapter 1
Quinoxaline–As a Parent Heterocycle



Quinoxaline

Quinoxalines are products of the spontaneous condensation of 1,2-diaminobenzene (1,2-DAB) with 1,2-dicarbonyl compounds (Scheme 1.1). The reaction was independently discovered many years ago by Hinsberg (1884) and Körner (1884).

Hinsberg suggested calling this series of compounds quinoxalines to point out their relationship with quinolines and the glyoxal—the dicarbonyl compound, from which the first representative of the series was obtained. Quinoxaline: [*Quin* (oline) + (gly)*oxal* + *ine*] (Hinsberg 1884).

Quinoxaline is a bicyclic heterocycle consisting of a benzene ring fused to a pyrazine, hence a quinoxaline is also called Benzo[*a*]pyrazine, Benzopyrazine, Benzoparadiazine, 1,4-Benzodiazine, Phenopiazine, Phenpiazine, Quinazine, and Chinoxalin. It is isomeric with quinazoline, phthalazine, and cinnoline.

quinazoline

phthalazine

cinnoline

At least five methods are currently used for the synthesis of quinoxaline **3** (R = H). The first and the principal method is based on the condensation of 1,2-DAB with two-carbon suppliers, such as glyoxal (Mirjalili and Akbari 2011; Rahmatpour 2012; Chandra Shekhar et al. 2014) (Scheme 1.2, Eq. 1), ethane-1,2-diol (Climent et al. 2012; Tang et al. 2015) (Scheme 1.2, Eq. 2), 2-aminoethanol (Tang et al. 2015) (Scheme 1.2, Eq. 3), 1,4-dioxane-2,3-diol (Venuti 1982) (Scheme 1.2, Eq. 4). The second method is based on the reaction of

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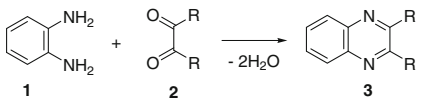
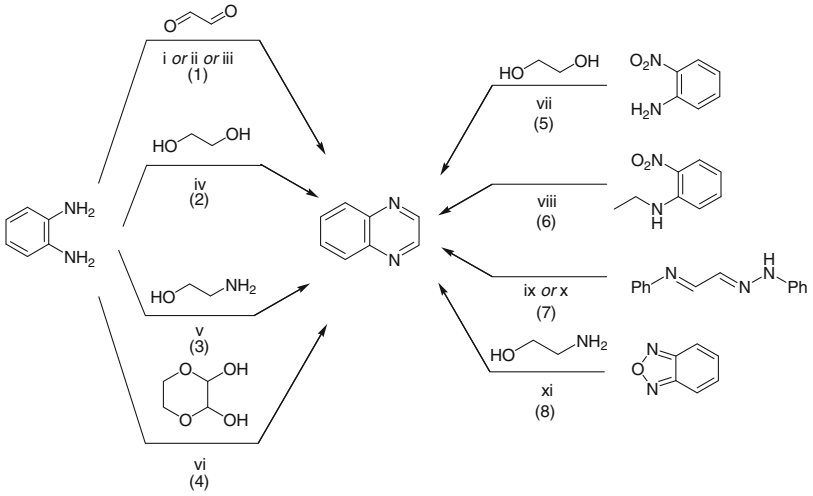


Scheme 1.1 Hinsberg and Körner synthesis of quinoxalines

2-nitroaniline with ethane-1,2-diol (Nguyen et al. 2015) (Scheme 1.2, Eq. 5). The third is the self-condensation of aniline derivatives, such as *N*-ethyl-2-nitroaniline (Walczak et al. 2015) (Scheme 1.2, Eq. 6) and *N*-[2-(2-phenylhydrazono)ethylidene]aniline (McNab 1980; Duffy et al. 2004) (Scheme 1.2, Eq. 7). The fourth method is based on the condensation of benzofurazan (benzo[*c*][1,2,5]oxadiazole) with 2-aminoethanol (Samsonov 2007) (Scheme 1.2, Eq. 8), and the fifth method is based on the redox processes of various quinoxaline derivatives (Hirasawa et al. 2008; Karki et al. 2013; Chelucci and Figus 2014; Cui et al. 2015; Jeong et al. 2015) (Scheme 1.3).

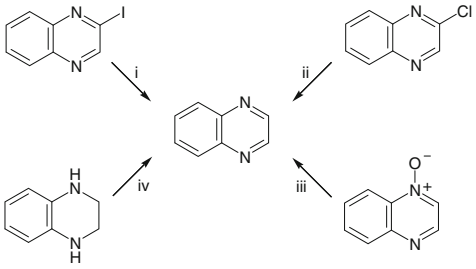
Quinoxaline **3** (R = H) is a light yellow to brown crystalline, water-soluble powder, with the molecular formula $C_8H_6N_2$ and the molar mass 130.15 g/mol. The



i = aq. HF, rt (98%)
ii = PS/$AlCl_3$ (10 mol%), EtOH, reflux (95%)
iii = nano-TiO_2, rt (88%)
iv = Au/CeO_2 (cat), diglime (91%)
v = $CsOH{\cdot}H_2O$, MS, 120 °C, 23 h, O_2 atmosphere (81%)
vi = EtOH, rt, 30 min (95%)
vii = $FeCl_3{\cdot}6H_2O$, $Na_2S{\cdot}nH_2O$, 180 °C, 24 h (67%)
viii = DMAC, toluene, K_2CO_3, 165 °C (5%)
ix = 600 °C, 0.01 Torr (35%)
x = 475 °C, 0.007 mbar, 35 min (78%)
xi = *p*-TsOH, 150-170 °C, 4 h (87%)
PS/$AlCl_3$ = Polystyrene-supported aluminium chloride
DMAC = *N,N*-Dimethylacetamide

Scheme 1.2 Current methods for the quinoxaline ring synthesis

Scheme 1.3 The use of quinoxaline derivatives in quinoxaline synthesis



i = In, water, reflux, 5.5 h (44%)
ii = $Pd(OAc)_2$, PPh_3, $NaBH_4$, TMEDA, THF (72%)
iii = $Cu(OTf)_2$, 1,2-DCE, MS 4Å, 60 °C, 12 h (81%)
iv = FeO*x*@NGr-C (cat), heptane, 15 bar air, 100 °C, 12 h (93%)
TMEDA = *N,N,N′,N′*-Tetramethylethylenediamine;
1,2-DCE = 1,2-Dichloroethane;
FeOx@NGr-C=Iron oxides surrounded by nitrogen-doped-graphene sh immobilized on carbon support

pK_a (Albert 1963) of quinoxaline in water at 20 °C is 0.60: it is therefore considerably a weaker base than the isomer diazanaphthalenes namely, cinnoline (pK_a 2.42), phtalazine (pK_a 3.47), and quinazoline (pK_a 1.95). Quinoxaline has the following physical properties: mp 29–32 °C, bp 220–223 °C, density 1.124 g/mL at 25 °C and flash point 209 °F TCC (98.33 °C) and is used mainly in organic synthesis.

The ^{1}H NMR spectrum of quinoxaline **3** (R = H) has been measured in DMSO-d_6. The signal for H(2) and H(3) of quinoxaline appears as an AA′BB′ system. The low-field half of the AA′BB′ multiplet is assigned to the protons H(5) and H(8) and the high-field half to the protons H(6) and H(7). Some broadening of the signals from protons 5 and 7 is attributed to long-range coupling with protons 2 and 3. The chemical shifts for protons 2 and 3, 5 and 8, and 6 and 7 are 8.97, 8.13–8.09, and 7.90–7.86 ppm (our result), respectively. As compared with the 8.85 (s, 2H), 8.17–8.05 (m, 2H), 7.84–7.72 (m, 2H) in $CDCl_3$ (Cui et al. 2015) and 8.83 (s, 2H), 8.10 (dd, J = 4.2, 2.3 Hz, 2H), 7.76 (dd, J = 4.2, 2.3 Hz, 2H) in $CDCl_3$ (Tang et al. 2015).

For a general introduction to quinoxaline chemistry as a parent heterocycle see Chap. II in "Condensed Pyrazines" by Cheeseman and Cookson (1979).

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Chapter 2
Synthesis of Quinoxalines

2.1 Introduction

The synthesis of quinoxalines has been intensively studied in the past, especially because of the diverse biological activities ascribed to many representatives of this class of compounds. Consequently, a large variety of synthetic methods for the synthesis of functionalized quinoxalines has been reported in literature. The first reports were published more than a century ago (Hinsberg 1884; Körner 1884), but even today chemists endeavor to create new and improved routes to these versatile compounds.

The synthesis and chemistry of quinoxalines have attracted considerable attention in the past 10 years (Porter 1984; Horton et al. 2003; Sherman et al. 2007; Patidar et al. 2011). The quinoxaline moiety is present in a large variety of physiologically active compounds, with applications varying from medicinal to agricultural. Various quinoxalines exhibit biological activities including antiviral (Westphal et al. 1977; Fonseca et al. 2004), in particular, against retroviruses such as HIV (Loriga et al. 1997; Balzarini et al. 2000; Rosner et al. 1998; Patel et al. 2000), antibacterial (Griffith et al. 1992; El-Sabbagh et al. 2009), antimicrobial (Sanna et al. 1999; Ali et al. 2000; Carta et al. 2001; Seitz et al. 2002; Badran et al. 2003; Singh et al. 2010), anti-inflammatory (Wagle et al. 2008; El-Sabbagh et al. 2009), antiprotozoal (Hui et al. 2006), anticancer (Monge et al. 1995a; Loriga et al. 1997; Lindsley et al. 2005; Carta et al. 2006), (colon cancer therapies) (LaBarbera and Skibo 2005), antidepressant (Sarges et al. 1990), antifungal (Loriga et al. 1997; El-Hawash et al. 1999; Carta et al. 2001), antituberculosis (Waring et al. 2002; Jaso et al. 2003; Ancizu et al. 2010), antimalarial (Rangisetty et al. 2001; Guillon et al. 2004), antihelmintic (Sakata et al. 1988), antidiabetic (Gupta et al. 2005), and as kinase inhibitors (Levitzki 2003; Lindsley et al. 2005). Additionally, they are used in the agricultural field as fungicides, herbicides, and insecticides (Sakata et al. 1988). Quinoxaline moieties are also present in the structure of various antibiotics such as echinomycin, levomycin, and actinoleutin, which are known to inhibit the

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growth of gram-positive bacteria and are active against various transplantable tumors (Dell et al. 1975; Kim et al. 2004). In addition, quinoxaline derivatives have found applications as dyes (Katoh et al. 2000; Sonawane and Rangnekar 2002; Jaung 2006), efficient electroluminescent materials (Thomas et al. 2005), in organic light-emitting devices (Fukuda et al. 1996; O'Brien et al. 1996; Wang et al. 2002; Kulkarni et al. 2005; Thomas et al. 2005), as fluorescent materials (Ahmad et al. 1996; Hirayama et al. 2005; Tsami et al. 2007), organic semiconductors (O'Brien et al. 1996; Dailey et al. 2001), chemically controllable switches (Crossley and Johnston 2002), building blocks for the synthesis of anion receptors (Sessler et al. 2002), cavitands (Castro et al. 2004), dehydroannulenes (Sascha and Rudiger 2004), and DNA-cleaving agents (Yamaguchi et al. 1998; Kazunobu et al. 2002; Hegedus et al. 2003; Patra et al. 2005). They also serve as useful rigid subunits in macrocyclic receptors in molecular recognition (Elwahy 2000; Mizuno et al. 2002; Kumar et al. 2008).

Besides these, quinoxalines have been identified as platforms for diversity-oriented synthesis on a solid phase (Lee et al. 1997; Zaragoza and Stephensen 1999), and they are established as inhibitors of aldose reductase (Sarges and Lyga 1988), agonists of the γ-aminobutyric acid A ($GABA_A$)/benzodiazepine receptor complex (TenBrink et al. 1994; Jacobsen et al. 1996), antagonists of the AMPA and angiotensin II receptors (Kim et al. 1993), antagonists of the selective human A3 adenosine receptor (Catarzi et al. 2005), antagonists of 5-HT3 receptors (Monge et al. 1993), growth inhibitors of *Trypanosoma cruzi* (Aguirre et al. 2004), in the growth inhibition of *Escherichia coli* (Takeda et al. 2005), in cyclooxygenase (COX-2) inhibitory activity (Singh et al. 2004), and as inhibitors of cholesteryl ester transfer protein (Jones et al. 2005; Eary et al. 2007).

A number of selected examples of biologically active quinoxalines chosen from an impressive list (Negwer and Scharnow 2001) are depicted in Fig. 2.1. Note: 'R' indicates the salt form of the drug; 'S' indicates the synonyms under which the drug is known; 'U' indicates its medicinal use; and 'P' indicates the page in reference (Negwer and Scharnow 2001).

As can be seen from the below data (Fig. 2.1) quinoxalines belong to a class of excellent heterocyclic scaffolds owing to their wide biological properties and diverse therapeutic applications in medicinal research. They are complementary in shapes and charges to numerous biomolecules they interact with, thereby resulting in increased binding affinity. The pharmacokinetic properties of drugs bearing quinoxaline cores have shown them to be relatively easy to administer either as intramuscular solutions, oral capsules, or rectal suppositories. Below (Figs. 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 2.8, 2.9, 2.10, 2.11, 2.12, 2.13, 2.14, 2.15, 2.16, 2.17 and 2.18) the recent advances in the synthesis (see papers referred to under the structures) and pharmacological diversities of quinoxaline motifs which might pave ways for novel drugs development are given.

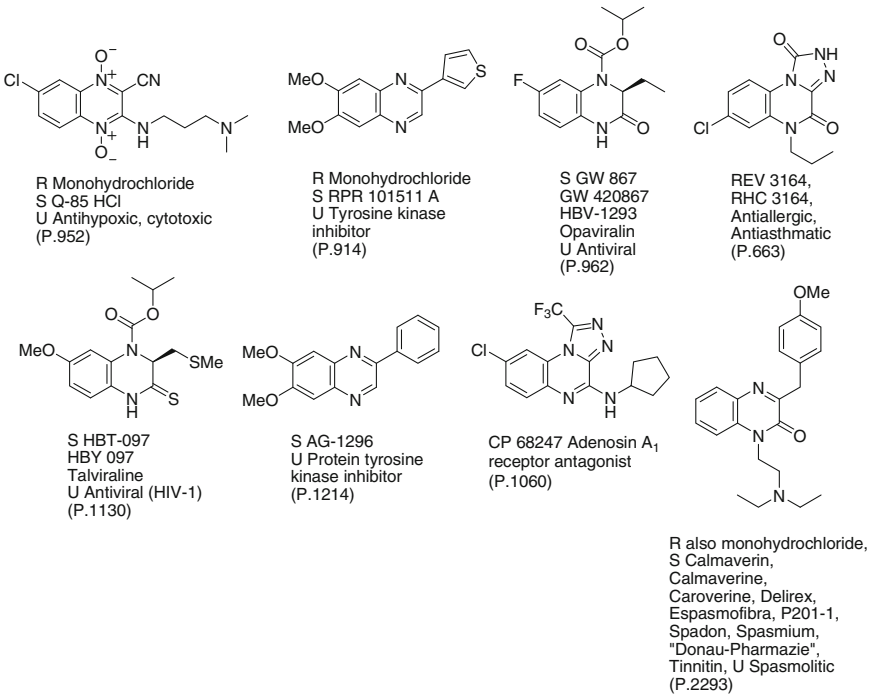
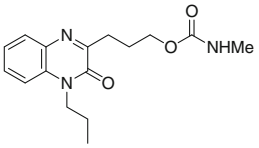
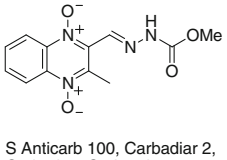


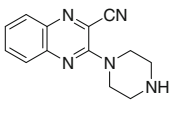
Fig. 2.1 Quinoxaline containing drugs and their synonyms



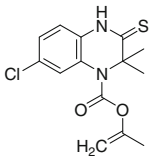
S Bamaquimast, L 004
U Anti-asthmatic
(P.1303)



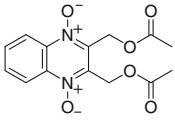
S Anticarb 100, Carbadiar 2,
Carbadox, Carbamix,
Enterodox, Enterosuis,
Fortigro, Getroxel,
GS-6244, Mecadox
U Antibacterial
(P.546)



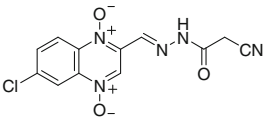
S VC 501
U Anti-emetic
(P.806)



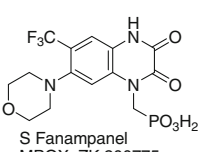
S 2720
U Antiviral
(P.942)



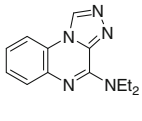
S Chinoxidin,
Chinoxydin,
Quinoxidin
U Antibacterial
(P.935)



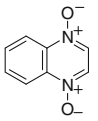
S Ciadox, Cyadox,
VUFB-11502
U Antibacterial
growth promotor
(veterinary)
(P.655)



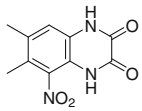
S Fanampanel
MPQX, ZK 200775
U Neuroprotectant
(AMPA receptor antagonist)
(P.944)



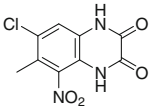
CP 41475
Antidepressant
CNS stimulant



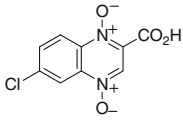
S Grofas ICI8173,
Quindoxin,
RD2579
U Growth promotor
(veterinary)
(P.237)



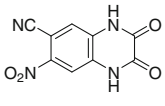
S ACEA 1328
U NMDA / glycine site
antagonist
(P.427)



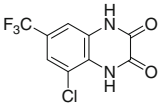
S ACEA 1416
U NMDA / glycine site
antagonist
(P.319)



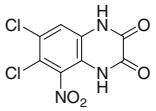
S MCD-819
U Antibiotic from
Streptomyces ambofaciens
MA2870 (P.317)
R Sodium salt (22587-19-5)



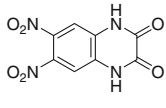
S CNQX, FG 9065
U Glutamate receptor
antagonist
(P.315)



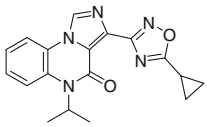
S ACEA 1011
U Glycine receptor
antagonist
(neuroprotective)
(P.315)



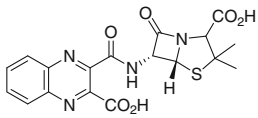
S ACEA 1021, Glystatine,
Licostinel
U NMDA receptor
antagonist
(neuroprotective) (P.233)



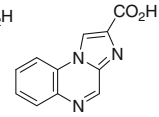
S DNQX, FG 9065
U non-DMDA receptor
antagonist
(P.234)



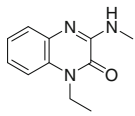
S FG 10571 NNC 14-0571
Panadiplon,
U 78875 anxiolytic
benzodiazepin receptor
partial agonist
(P.1545)



S Chinacillina, Quinacillin
R.D. 13962
U Antibiotic
(P.1535)

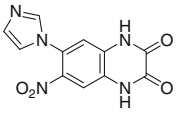


S Dazoquinast P.
Anti-allergic
(P.533)

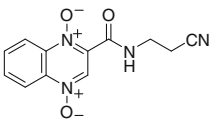


S Ataquimast,
Tinamast
U Tumor
necrosis factor
antagonist
(P.581)

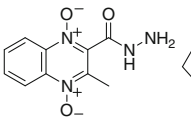
Fig. 2.1 (continued)



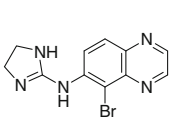
R Monohydrochloride
S YM-90K, YM-900
U Neuroprotective
(AMPA antagonist)
(P.533)



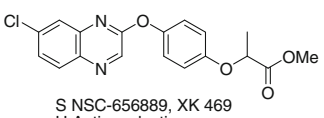
S CGA 56766 Cinoquidox
U Antibacterial
growth promotor (veterinary)
(P.800)



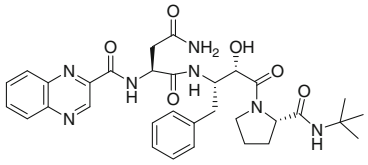
S Drazidox
U Antiseptic
(P.437)



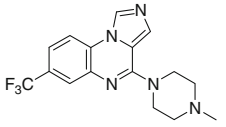
R D-Tartrate (1:2)
S AGN 190342-LF
Alphagan
Brimonidine tartratr
UK-14304-18
U Antihypertensive
Antiglaucoma agent
(α_2-adrenoceptor agonist)
(P.542)



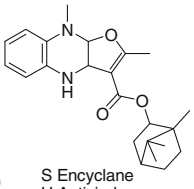
S NSC-656889, XK 469
U Antineoplastic
(P.1526)



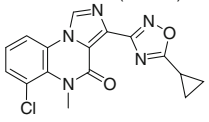
S R 87366
U Antiviral
(P.2999)



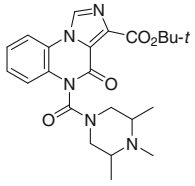
R Maleate(1:2)
S CGB 12066B
U (Serotonin-1B agonist)
(P.1393)



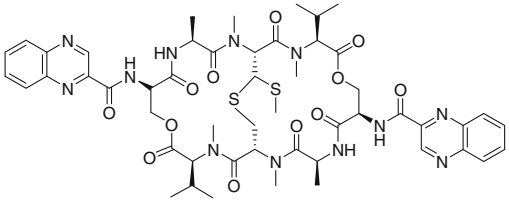
S Encyclane
U Antiviral
(P.2446)



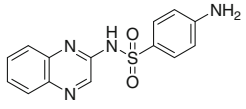
S U-80447
U Antidepressant
Anxiolytic
(P.1191)



S U 97775
U Anxiolytic
($GABA_A$ receptor ligand)
(P.2442)

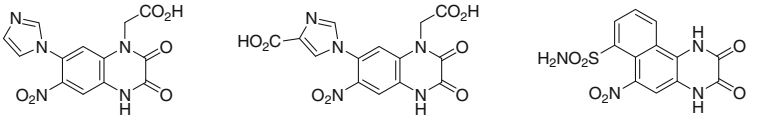


S Ehinomycin, NSC-526417, Quinomycin A
U Antineoplastic antibiotic
(P.3218)



R also monosodium salt,
S Anticox, Apokina, Avicocid,
Aviochina, Benachinossalina,
Biococcid, Biocrin S, Chinovit L,
Chinoxal, Coccidione,
Coccidioxal, Coccistop,
Coccisulfa, Compound 3-120,
Coxine 200, Deidrochin L,
Embazin, Italquina, Izochinossal,
Kinocond, Kokozigal S, Liquicox,
Med-Solvimix, Nococcin, Oxalin 100,
Quinoxal, Quinoxipra-C,
Solaquin Un Comm. Lombarda,
Solucoccid, SQX,
Sulfabenzpyrazinium,
Sulfachinossalina,
Sulfachinoxalin, Sulfox,
Sulfoxin, Sulfaquinoxaline,
Sul-Q-Nox, Sulquin,
Ursokoxalin, U Coccidiostatic
(P.916)

Fig. 2.1 (continued)

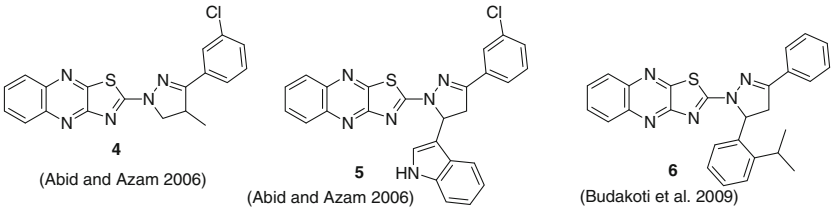


1 (YM872)
(Mattes et al. 2010)

2 (LU112313)
(Olayiwola et al. 2007)

3 (NBQX)
(Löscher et al. 1999; Olayiwola et al. 2007)

Fig. 2.2 Antibiotic and AMPA receptor antagonists containing quinoxaline core structures



4
(Abid and Azam 2006)

5
(Abid and Azam 2006)

6
(Budakoti et al. 2009)

7
(Duque-Montano et al. 2013)

8
(Lopez-Vallejo et al. 2011)

9
(Lopez-Vallejo et al. 2011)

Fig. 2.3 Some quinoxaline motifs with antiamoebic activity

Thus quinoxaline derivatives are crucial structural scaffolds found in diverse library of compounds which are therapeutically useful agents in medicinal chemistry research. A constant analysis into chemistry and biodiversity relevance of quinoxaline is inevitable for its pharmacological influence. Above data unveiled numerous biological applications of quinoxaline-based scaffolds offering excellent pathways to new biomolecular targets which qualify them to be excellent precursors in drug design and future candidates in therapeutic research. It also demonstrated that a continuous explorative study into the world of quinoxaline cannot be overemphasized, if mankind wants to stay healthy and live free of infection. This is because it provides resourceful tool of information for synthetic modifications of old existing quinoxaline-based drugs in order to tackle drug resistance bottlenecks in therapeutic medicine.

This diversity of useful synthetic quinoxaline derivatives accounts for the appearance of modifications of the classical synthetic methods and for the search for new methods ensuring the availability of the corresponding functionalized quinoxalines.

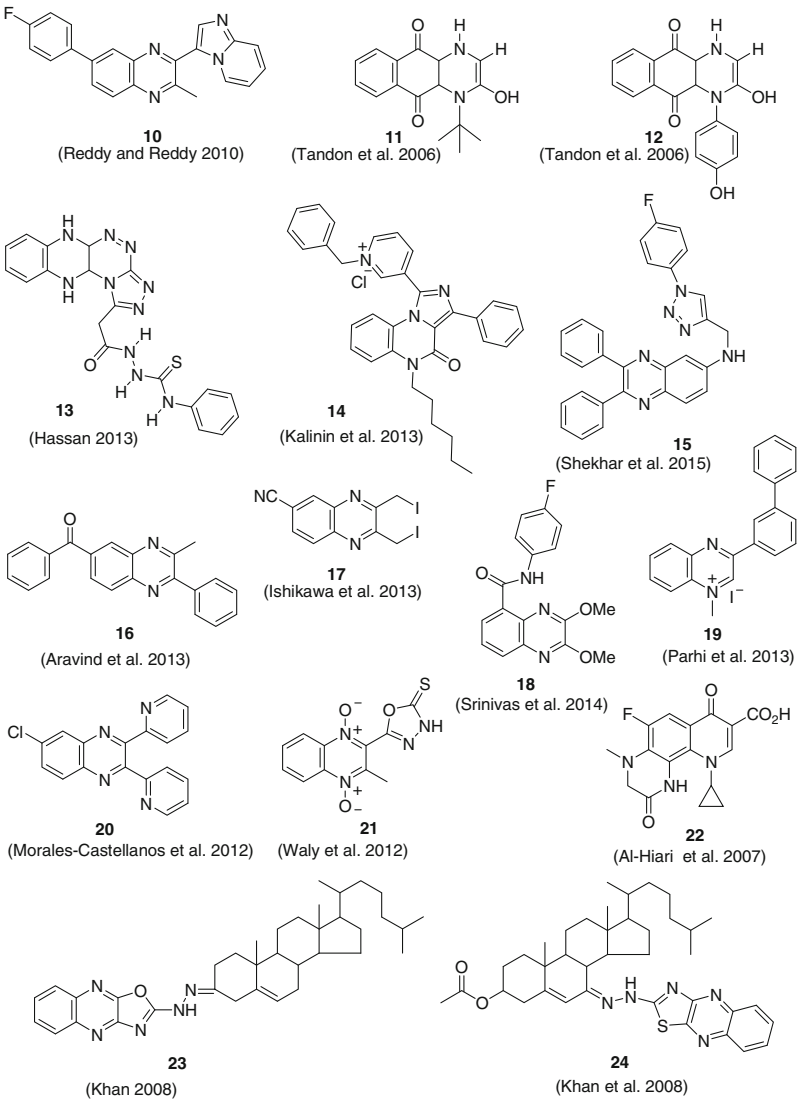


Fig. 2.4 Some quinoxaline motifs with antibacterial activity

In this chapter, a comprehensive overview of the different synthetic methodologies leading to functionalized quinoxalines and their di-, tetra-, and hexahydro derivatives will be given. These methodologies are based on the five main approaches to the synthesis of quinoxalines: condensation of 1,2-diaminobenzenes (1,2-DABs) with various two-carbon unit donors, cyclization of aniline derivatives,

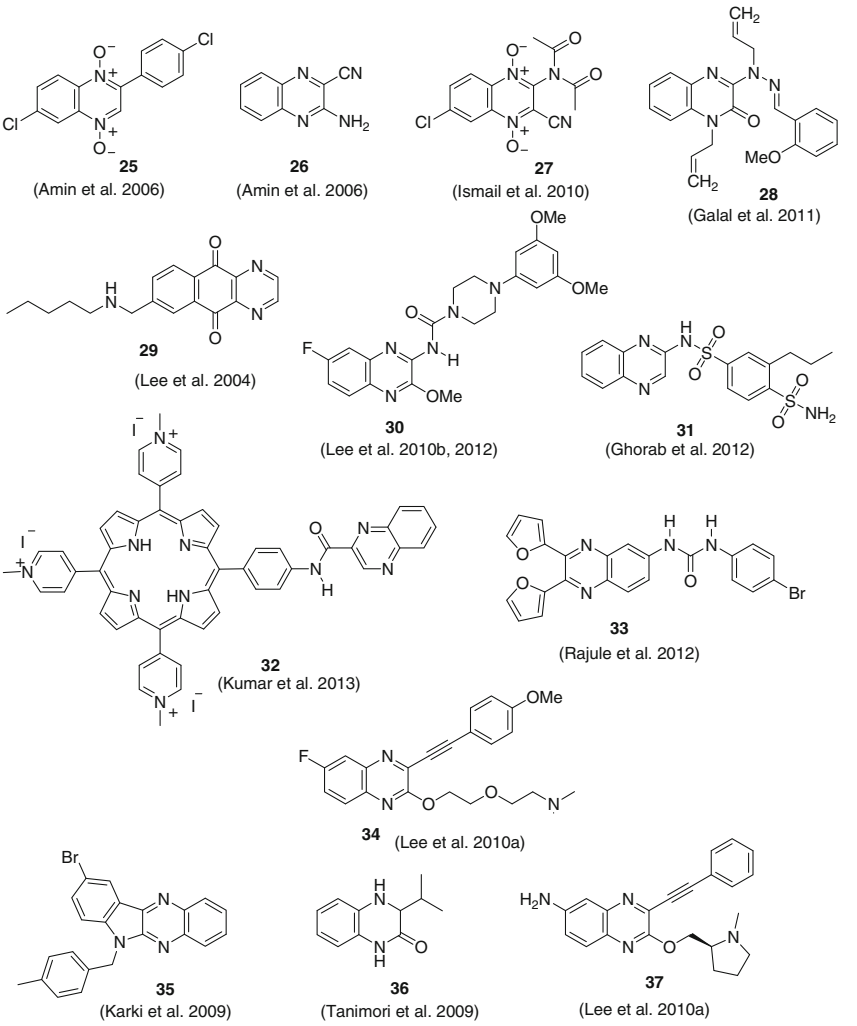


Fig. 2.5 Some quinoxaline motifs with anticancer activity

and reactions of various heterocyclic systems devoid of a pyrazine fragment and with heterocyclic systems containing a pyrazine fragment.

The synthesis of fused and polycyclic derivatives of quinoxalines will not be dealt with in this chapter, except those cases where the formation of these systems occurs in one pot. This implies either the condensed parent compounds or the compounds capable, besides constructing a quinoxaline system, to annulate separate rings on various sides under the reaction conditions.

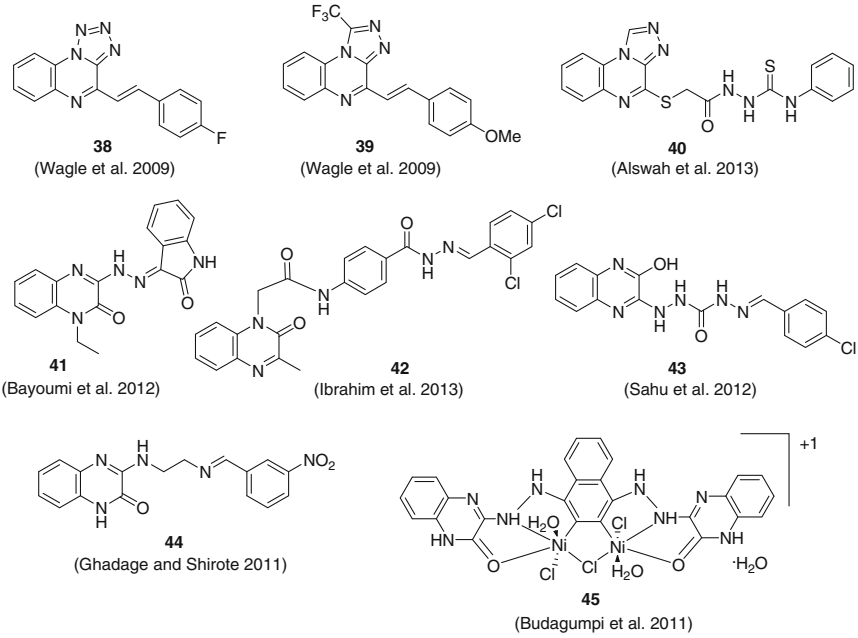


Fig. 2.6 Some quinoxaline motifs with anticonvulsant activity

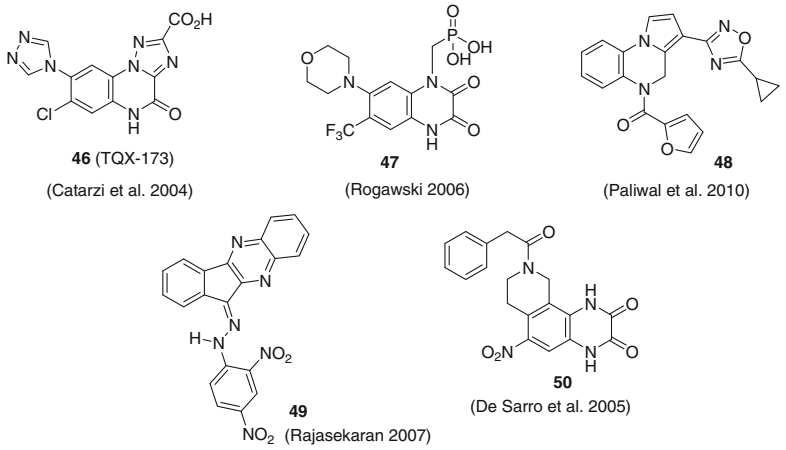


Fig. 2.7 Some quinoxaline motifs with antiepileptic activity

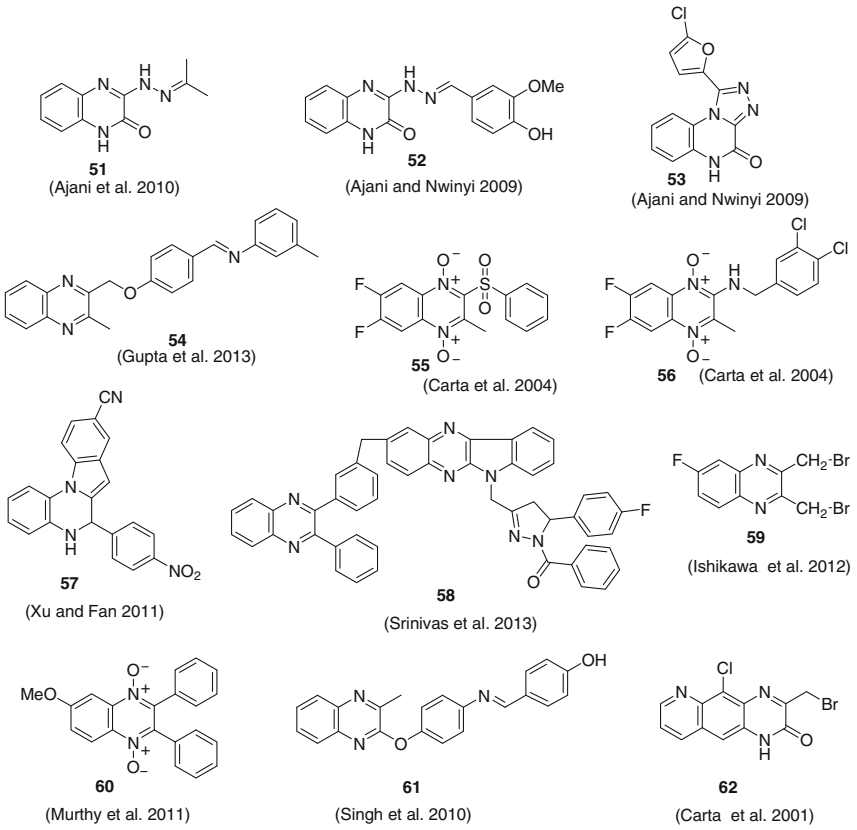


Fig. 2.8 Some quinoxaline motifs with antifungal activity

2.2 Condensation of 1,2-Diaminobenzenes (1,2-DABs; *Ortho*-Phenylenediamines) and Derivatives with Various Two-Carbon Unit Suppliers

2.2.1 With Pyruvates (2-Oxopropanoates)

The reaction of pyruvates with 1,2-DABs, first discovered by Hinsberg (1884, 1887) and Körner (1884) many years ago, independently of one another, is still the most appropriate method for the synthesis of 3-substituted quinoxalin-2(1*H*)-ones (Abasolo et al. 1987; Piras et al. 2006; Eller et al. 2007; El-Sabbagh et al. 2009; Yuan et al. 2009; Singh et al. 2010). A kinetic study of the Hinsberg reaction involved reacting unsymmetrical 1,2-DABs with pyruvates and the formation of

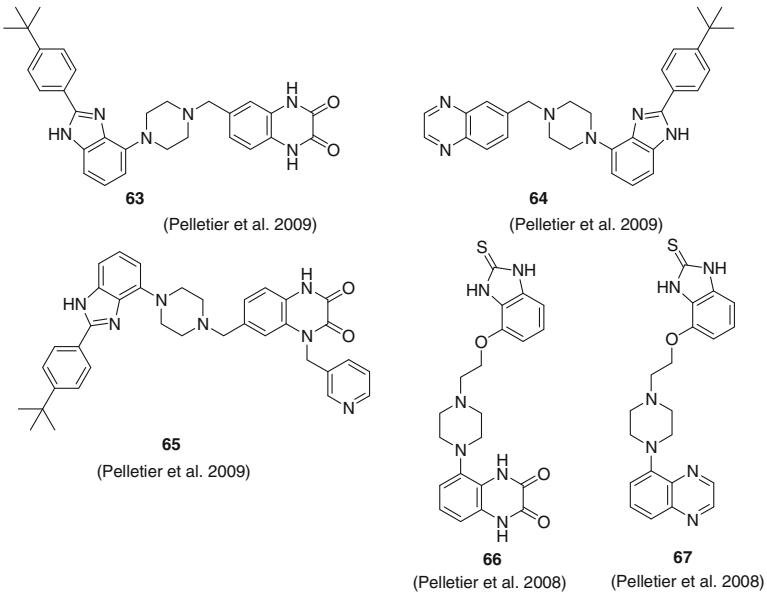


Fig. 2.9 Some quinoxaline motifs with GnRH antagonist activity

isomeric quinoxalin-2(1*H*)-ones (Abasolo et al. 1987). Some related compounds were synthesized in acetic acid to improve the regioselectivity (Lumma et al. 1981). The reaction of *N*-methyl-1,2-DAB with pyruvic acid, unlike the reactions of unsymmetrical 1,2-DABs, proceeds with the formation of 1,3-dimethylquinoxalin-2(1*H*)-ones as the sole products (Lawrence et al. 2001). Recently, a one-pot synthesis of polyfunctionalized dihydroquinoxalinone derivatives via the anti-Michael reaction has been developed (Ballini et al. 2009). Six quinoxalinone and three benzoquinoxalinone derivatives were obtained by using *S. cerevisiae* as a biocatalyst and also by means of microwave-assisted approaches (Gris et al. 2008). In general, most of these methods involve the use of toxic/volatile organic solvents with long reaction times, poor yields, and tedious product isolation procedures.

Nageswar and coworkers developed a facile and expeditious synthesis of 3-substituted quinoxalin-2(1*H*)-ones in water under catalyst-free conditions (Murthy et al. 2010). 3-Substituted quinoxalin-2(1*H*)-ones **158** are obtained when the pyruvic esters **156** or the phenylglyoxylate **157** are used in reaction with 1,2-DABs **155a–c** (Scheme 2.1) (Murthy et al. 2010).

While ethyl glyoxalate **159** and terminal alkynes **160** were used instead of pyruvic esters **156**, or phenyloxalate **157,** a novel and efficient protocol for the copper(II) catalyzed synthesis of furoquinoxalines **161–163** from readily available 1,2-DABs **155a–h** has been developed (Naresh et al. 2014) (Scheme 2.2).

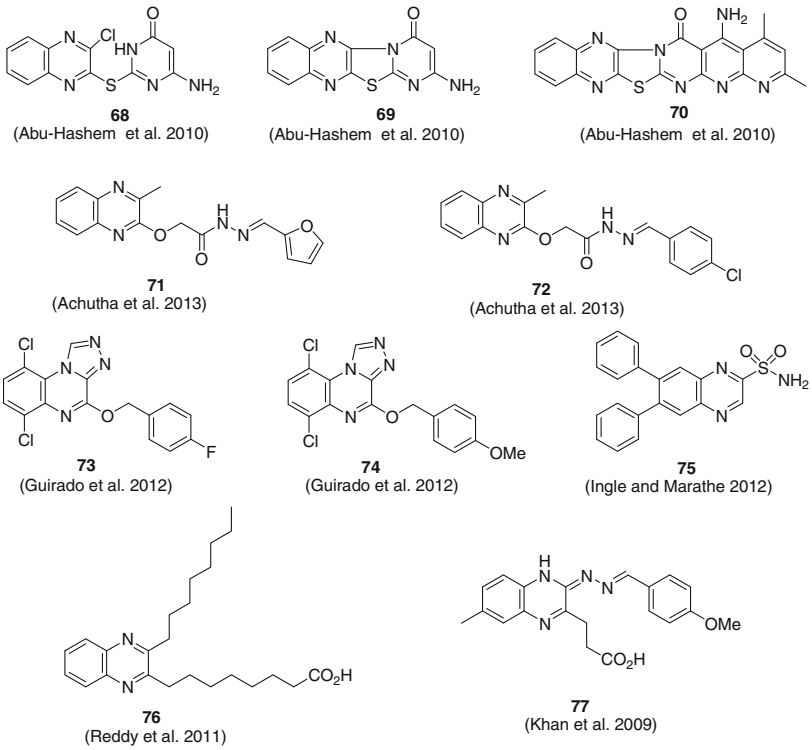


Fig. 2.10 Some quinoxaline motifs with anti-inflammatory and analgesic activities

A possible reaction mechanism for the formation of furoquinoxalines appears to be the tandem C–C bond formation followed by a *5-endo-dig* cyclization reaction as outlined in Scheme 2.3. Generally, in A3-coupling reactions, the amine **155a** reacts with aldehyde **159** and forms the imine which is further transformed to iminium ion **A**; at the same time the in situ generated copper acetylide **B** from terminal alkyne and copper(II) trifluoromethanesulfonate attacks the intermediate **A** to produce the propargylamine **C** (Peshkov et al. 2012). The resulting propargylamine **C** further attacks the ester functionality intramolecularly, leading to the generation of intermediate **D**. Since intermediate **D** is easily enolizable in an acidic medium, it provides the cyclized intermediate 3-(alkynyl)-3,4-dihydroquinoxalin-2(1*H*)-one **E** and a further cleavage of the metal π-complex occurs followed by oxidation furnishing the target furoquinoxaline.

This novel method involves the formation of four new bonds (2C–C, C–N, and C–O) in a cascade pathway.

A new and effective procedure was developed for the synthesis of 3-ethylquinoxalin-2(1*H*)-one from 1,2-DAB **155a** and ethyl 2-oxobutanoate

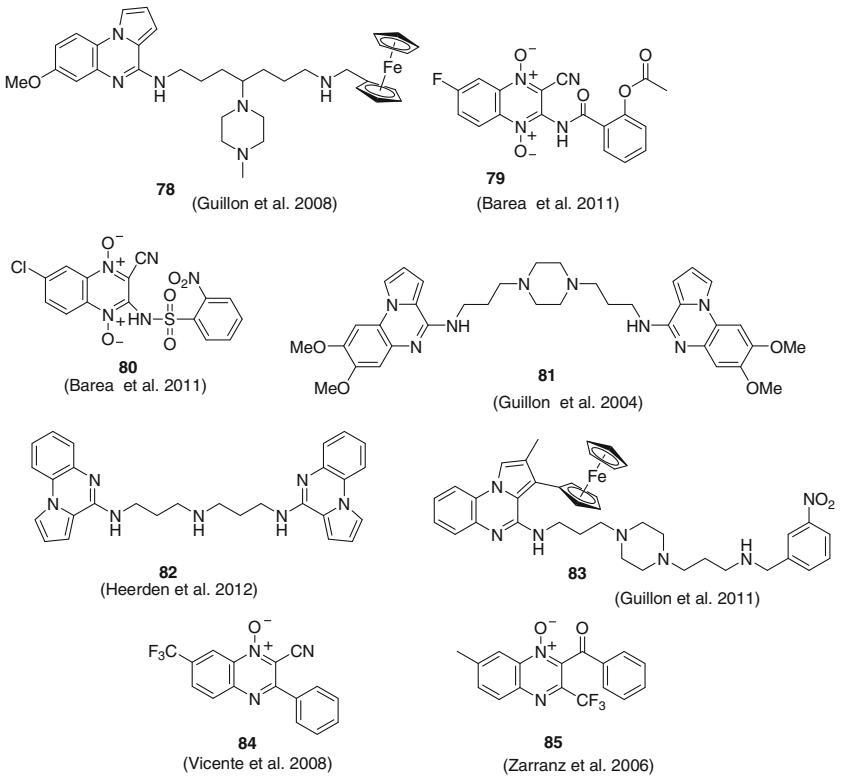


Fig. 2.11 Some quinoxaline motifs with antimalarial activity

(Mamedov et al. 2005). The latter was prepared by the Grignard reaction of diethyl oxalate with ethylmagnesium bromide or iodide. 3-Functionally substituted quinoxalin-2(1*H*)-ones can also be synthesized by the functionalization of an alkyl group at C(3) of quinoxalin-2(1*H*)-ones. For example, the functionalization of quinoxalinone **165** was performed via the substitution of the bromine atom in α-bromoethyl derivative **166** when acted upon by various nucleophiles (Scheme 2.4) (Mamedov et al. 2005). Compound **166** is readily obtained by the treatment of a suspension of **165** in 1,4-dioxane with bromine at 12–15 °C. The bromine atom in **166** is readily replaced by such nucleophiles as KSCN, $PhNH_2$, and NaN_3 in DMSO to give the corresponding 3-(α-ethyl)quinoxalines **167–169**. Both the treatment of 3-(α-azidoethyl)quinoxaline **169** with a 70 % aqueous acetic acid and the direct oxidation of quinoxalinone **165** with chromic anhydride in 95 % acetic acid proceed with the formation of ketone **170** as the major product (Scheme 2.4) (Mamedov et al. 2005).

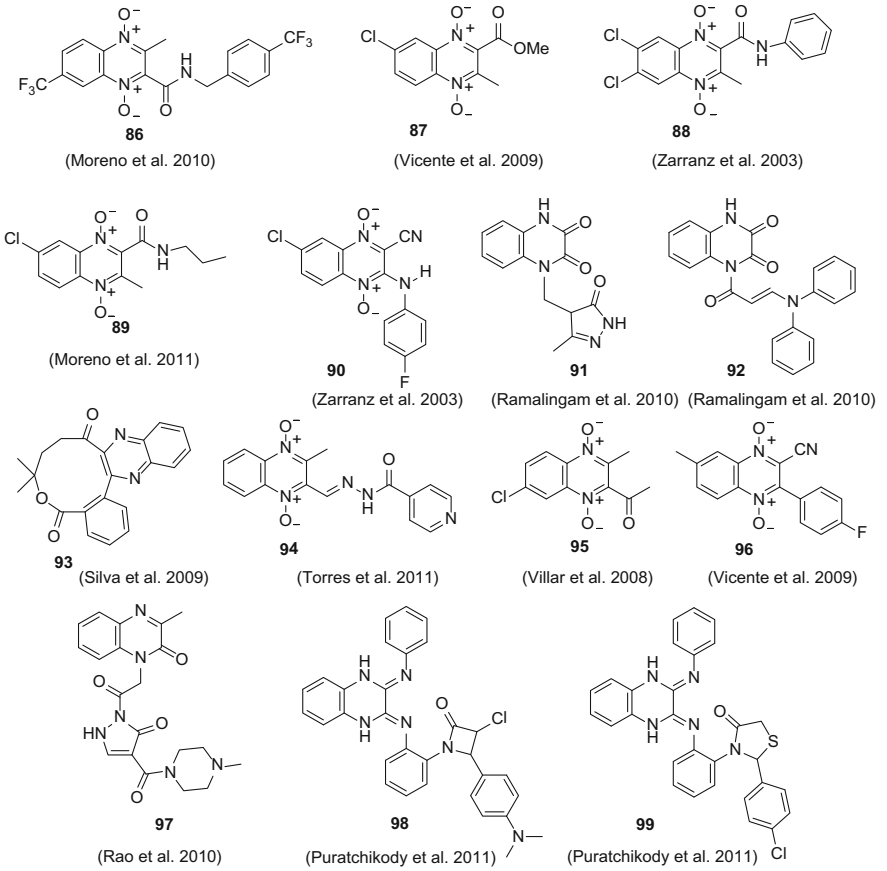


Fig. 2.12 Some quinoxaline motifs with antitubercular activity

Later the same strategy, using Cr_2O_3 in AcOH, was applied for oxidizing the methylene group of three 3-benzylquinoxalin-2(1*H*)-ones (Piras et al. 2006).

The cyclocondensation of equimolar amounts of 1,2-cyclohexanediamine (1,2-DACH) **171a** and ethyl pyruvate **156a** in a hot EtOH solution containing a catalytic amount of AcOH proceeds with the formation of 3-methyl-4*a*,5,6,7,8,8*a*-hexahydro-2(1*H*)-quinoxalinone **172** (Scheme 2.5) (El-Sabbagh et al. 2009). The coupling of the latter with an equimolar amount of diazonium salts **173** at 0 °C in AcOH, buffered with NaOAc, provided the novel hydrazones **174**. A good yield of ester **175** was obtained through the reaction of 1,2-DACH **171a** with diethyl oxaloacetate **156d** in EtOH containing AcOH at 80 °C and then at room temperature.

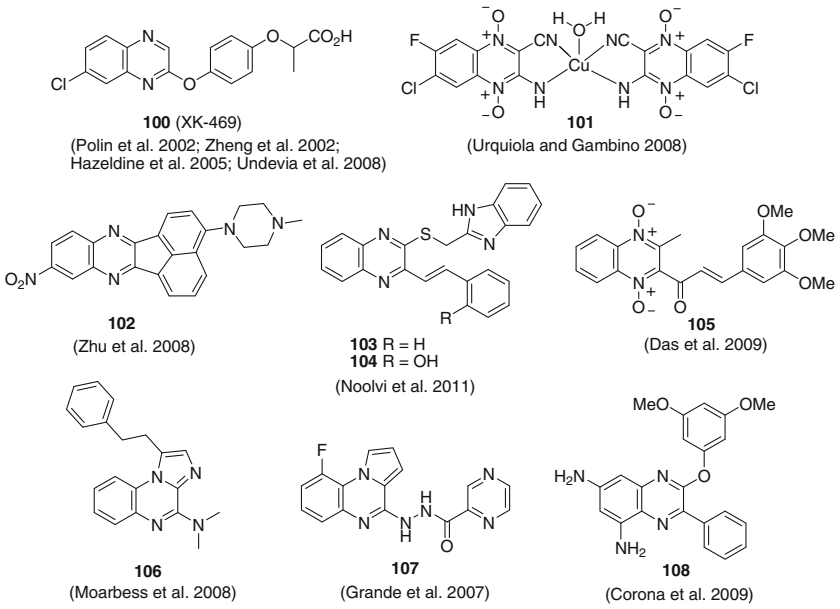


Fig. 2.13 Some quinoxaline motifs with antitumor activity

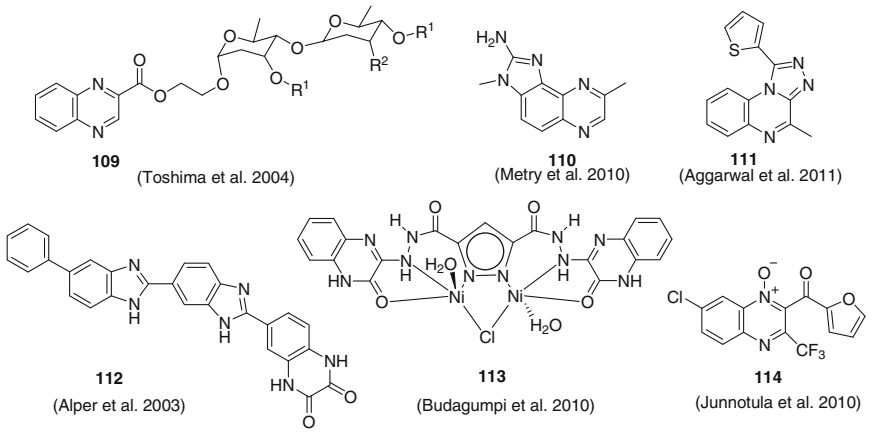


Fig. 2.14 Some quinoxaline motifs with DNA-cleavage properties

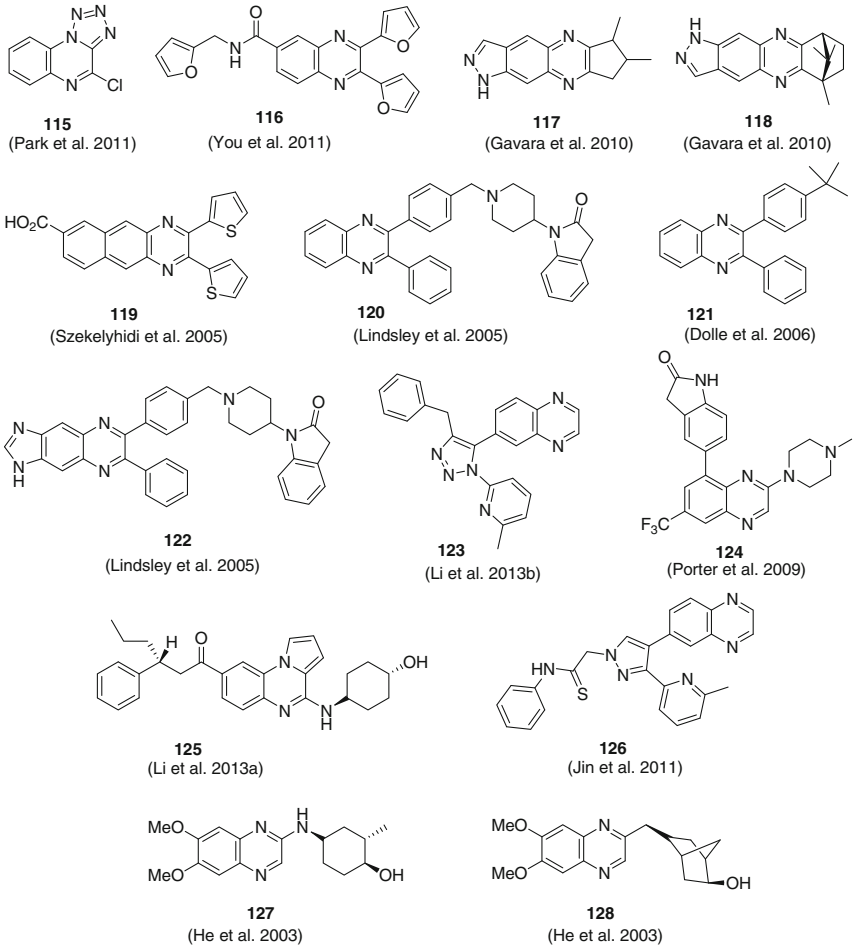


Fig. 2.15 Some quinoxaline motifs with kinase inhibitory activity

The hydrazide **176** was obtained through condensation of the ester **175** with hydrazine hydrate by heating the reactants in EtOH at reflux. Hydrazide **176** was used for synthesizing other functionalized derivatives of hexahydroquinoxalin-2 (1*H*)-one **175** (El-Sabbagh et al. 2009).

Diethyl ketomalonate (diethyl mesoxalate) **177** reacts with 1,2-DAB **155a** in the same way as do pyruvates to provide 3-ethoxycarbonyl quinoxalin-2(1*H*)-one **178** (Scheme 2.6) (Mahesh et al. 2011).

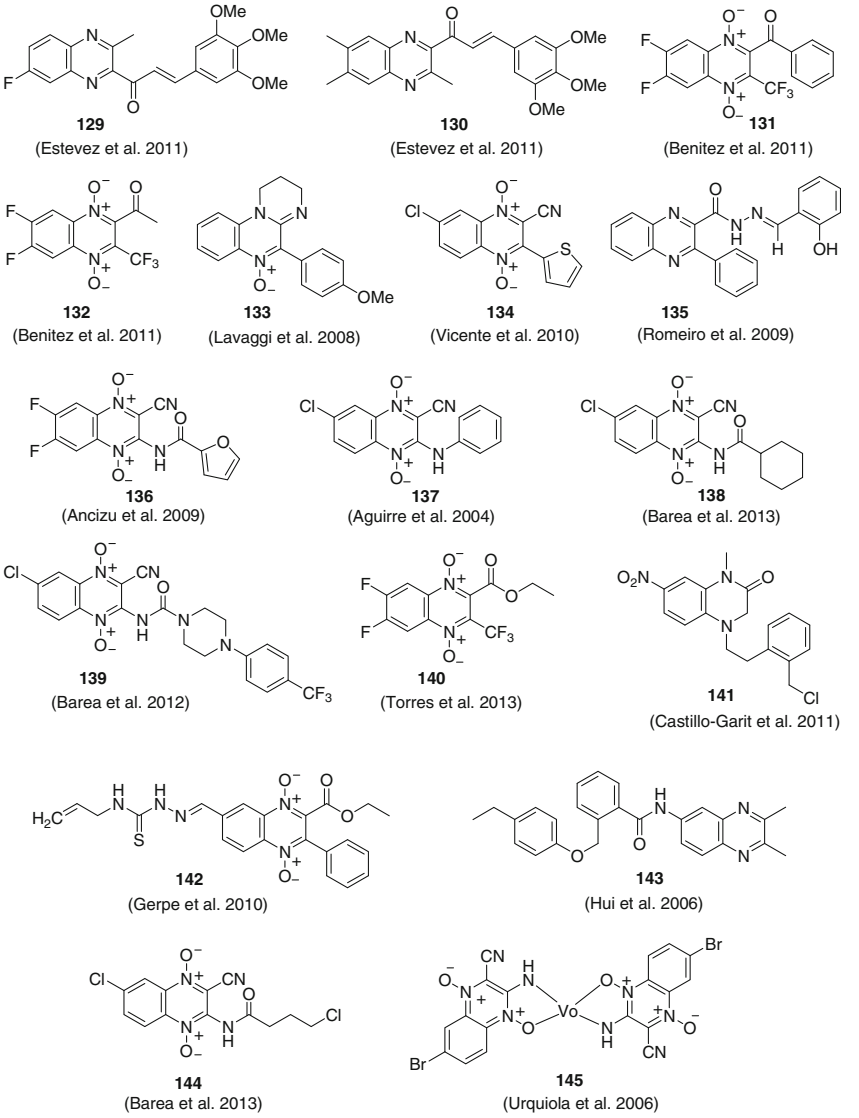


Fig. 2.16 Some quinoxaline motifs with trypanocidal properties

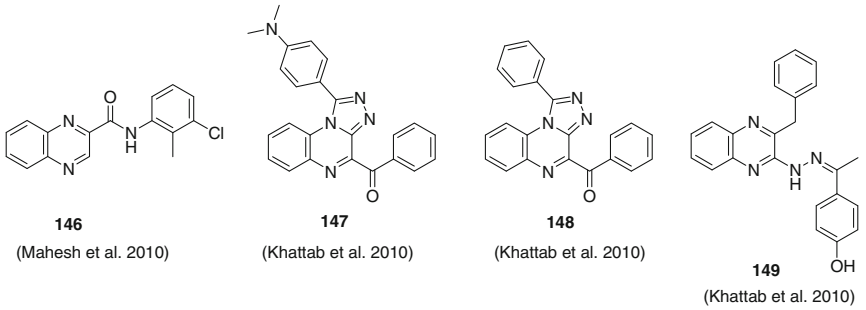


Fig. 2.17 Some quinoxaline motifs with antidepressant activity

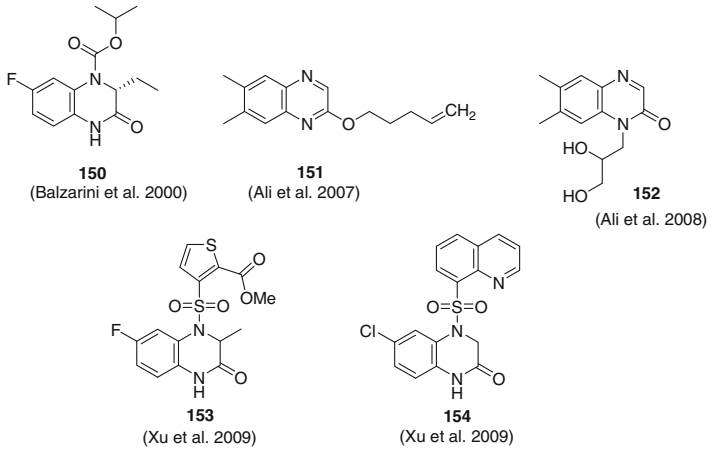
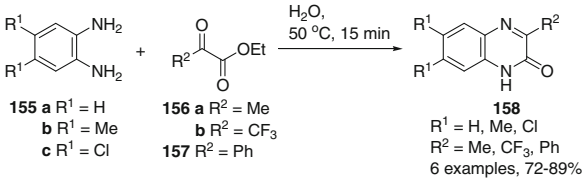


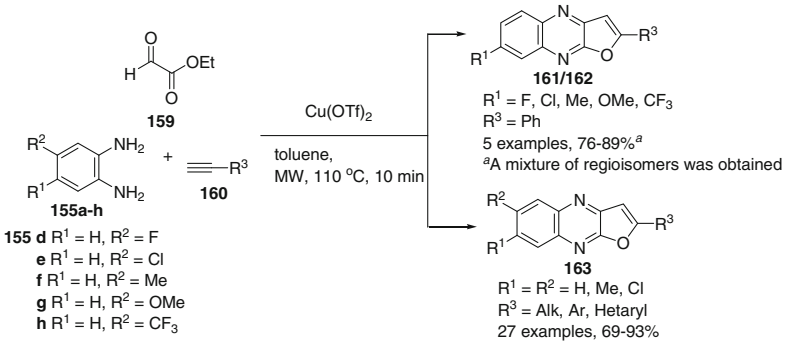
Fig. 2.18 Some quinoxaline motifs with anti-HIV activity

Scheme 2.1 Synthesis of 3-substituted quinoxalin-2 (1*H*)-ones **158** in H_2O under mild conditions

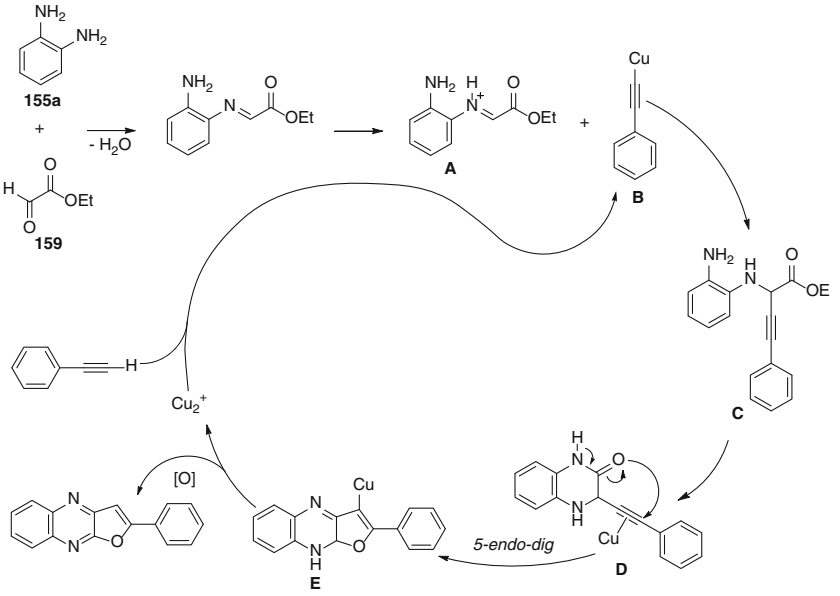


2.2.2 *With α-Diketones (1,2-Diketones)*

There are many examples of quinoxalines being prepared from α-diketones (1,2-diketones) usually involving the reaction of 1,2-DABs in refluxing ethanol or acetic acid (Carta et al. 2003; Fonseca et al. 2004; Hui et al. 2006; Wang et al. 2006;

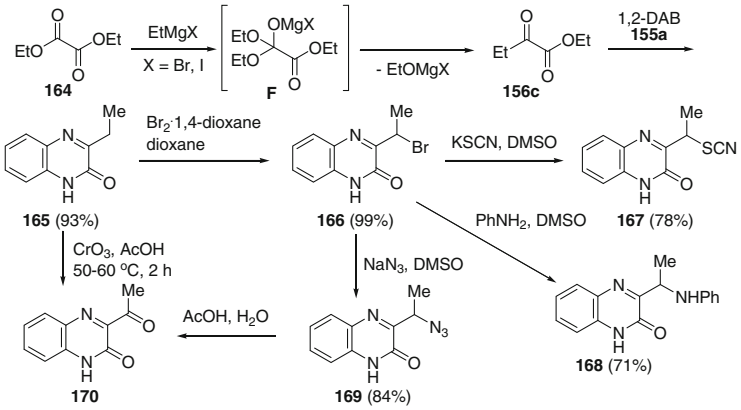


Scheme 2.2 Substrate scope for the synthesis of furoquinoxalines **161–163** with terminal alkynes under optimized conditions

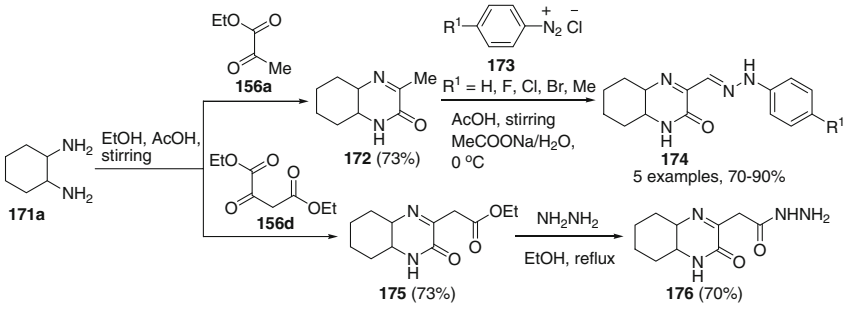


Scheme 2.3 Possible reaction mechanism for the tandem A3-coupling and 5-*endo-dig* cyclization

Tingo li et al. 2011; Xu et al. 2011a; You et al. 2011). Various catalysts, such as graphite (Kadam et al. 2013), bismuth(III) triflate (Yadav et al. 2008), metal hydrogen sulfates (Niknam et al. 2008), gallium(III) triflate (Cai et al. 2008), molecular iodine (Bhosale et al. 2005; More et al. 2005), cerium(IV) ammonium nitrate (More et al. 2006), stannous chloride (Shi et al. 2008), manganese(II) chloride (Heravi et al. 2008), zirconium tetrakis(dodecylsulfate) (Hasaninejad et al.

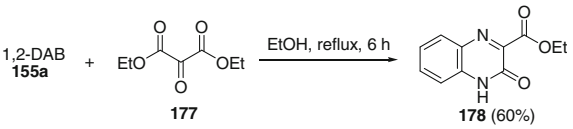


Scheme 2.4 The synthesis and side-chain functionalization of 3-ethylquinoxalin-2(1*H*)-one **165**



Scheme 2.5 Synthesis of hexahydro-2(1*H*)-quinoxalinones **172**, **174**, **175,** and **176**

Scheme 2.6 Synthesis of 3-ethoxycarbonyl quinoxalin-2(1*H*)-one **178**



2009), zirconium(IV) chloride (Aghapoor et al. 2010), niobium(V) chloride (Hou et al. 2010), silica-supported antimony(III) chloride ($SbCl_3/SiO_2$) (Darabi et al. 2009), silica-bonded *S*-sulfonic acid (SBSSA) (Niknam et al. 2009), silica sulfuric acid (SSA) (Shaabani and Maleki 2007), cellulose sulfuric acid (CSA) (Shaabani et al. 2009), amidosulfonic acid (Li et al. 2008), *p*-TsOH (Shi and Dou 2008), montmorillonite K-10 (Huang et al. 2008), zinc chloride-exchanged K10-montmorillonite (Zn^{2+}-K10-clay) (clayzic) (Dhakshinamoorthy et al. 2011), binary metal oxides supported on Si-MCM-41 mesoporous molecular sieves (Ajaikumar and Pandurangan 2009), polyaniline-sulfate salt (Srinivas et al. 2007, 2008), Wells–Dawso-type heteropolyacid ($H_6P_2W_{18}O_{62}\cdot 24H_2O$) (Heravi et al.

2007), Keggin-type heteropolyacid ($H_4SiW_{12}O_{40}$) (Huang et al. 2009), ionic liquid 1-*n*-butylimidazolium tetrafluoroborate (Potewar et al. 2008), Brönsted acid ionic liquid [$(CH_2)_4SO_3HMIM$][HSO_4] (Beheshtiha et al. 2010), nano-TiO_2 (Mirjalili and Akbari 2011), TiO_2–P25–SO_4^{2-} (Krishnakumar and Swaminathan 2010), TiO_2–SO_4^{2-} (Krishnakumar et al. 2010), acidic Al_2O_3 (Jafarpour et al. 2011), ZnO-beta zeolite (Katkar et al. 2010), LiBr (Hasaninejad et al. 2010), NH_4Br (Raju et al. 2009), Amberlyst-15/H_2O (Liu et al. 2010), PEG-400 (Zhang et al. 2010), and $KHSO_4$ (Oskooie et al. 2007), have all been used to promote this transformation.

A facile and simple catalyst-free protocol has been developed for the condensation of 1,2-diketones with 1,2-DABs in polyethylene glycol (PEG), providing quinoxaline derivatives in good yields (Huang et al. 2013). The important features of the methodology are broad substrates scope, simple workup, catalyst free, environmentally benign, and no requirement for metal catalysts. It is noteworthy that the cyclization reaction of 1,2-diketones with aliphatic 1,2-diamines is also conducted smoothly to afford pyrazines in good yields under the standard conditions (Huang et al. 2013). In addition, PEG could be recovered easily and was reused without evident loss in activity.

In order to reduce the reaction time and increase the yields of the quinoxalines, microwave irradiation methods have recently been extensively used (Zhao et al. 2004; Zhou et al. 2009; Bandyopadhyay et al. 2010; Zare et al. 2010).

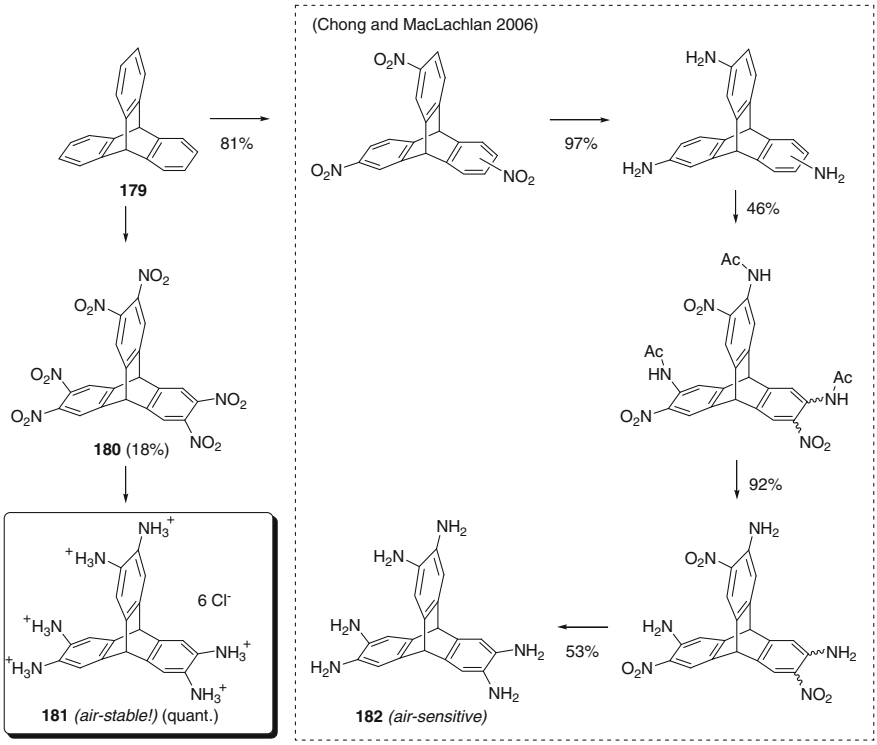
When symmetric α-diketones and symmetric 1,2-DAB derivatives and unsymmetric α-diketones and symmetric 1,2-DAB derivatives, and vice versa, have been used, the symmetric α-diketones and unsymmetric 1,2-DAB derivatives always exclusively produce one regioisomer (Carta et al. 2003; Zhao et al. 2004; Bhosale et al. 2005; More et al. 2005; Hui et al. 2006; Wang et al. 2006; Heravi et al. 2007, 2008; Oskooie 2007; Huang et al. 2008, 2009; Cai et al. 2008; Li et al. 2008, 2011; Shi and Dou 2008; Srinivas et al. 2008; Darabi et al. 2009; Niknam et al. 2009; Raju et al. 2009; Shaabani et al. 2009; Ajaikumar and Pandurangan 2009; Aghapoor et al. 2010; Bandyopadhyay et al. 2010; Beheshtiha et al. 2010; Hasaninejad et al. 2010; Liu et al. 2010; Katkar et al. 2010; Hou et al. 2010; Krishnakumar and Swaminathan 2010; Krishnakumar et al. 2010; Zare et al. 2010; Zhang et al. 2010; Jafarpour et al. 2011; Mirjalili and Akbari 2011; Tingoli et al. 2011; You et al. 2011). A similar situation was observed with unsymmetric diketones and unsymmetric 1,2-DAB derivatives. In this case the reactions proceed with the formation of mainly one (Hui et al. 2006; Bandyopadhyay et al. 2010; Mirjalili and Akbari 2011) and occasionally two products (Klein et al. 2001), although one could expect the formation of four possible regioisomeric quinoxalines. This selectivity is due to activation and deactivation of the nucleophilic ability of the amino group, and of the electrophilicity of that carbonyl carbon atom, which are involved in the first step of the condensations (Hui et al. 2006; Bandyopadhyay et al. 2010).

Instead of the simple α-dicarbonyl compounds and 1,2-DAB derivatives for the synthesis of quinoxalines (or compounds containing quinoxaline fragments), one can envisage that (a) fused compounds containing the α-dicarbonyl moiety with simple 1,2-DABs, (b) fused compounds containing a 1,2-diamino moiety and

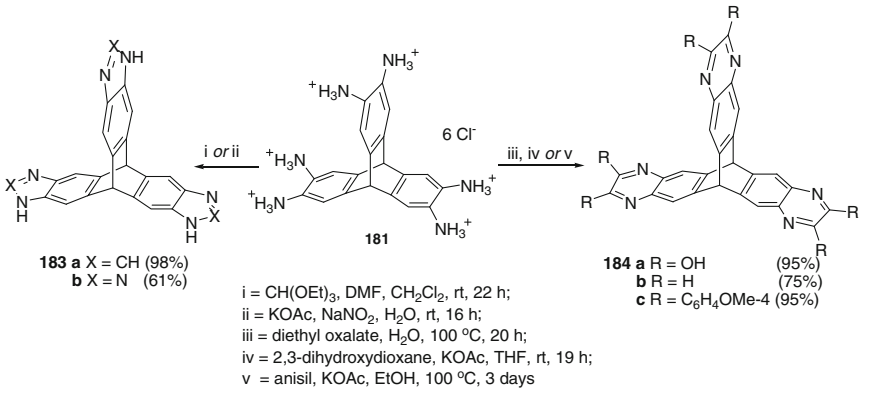
normal α-dicarbonyl compounds, and (c) fused compounds containing α-dicarbonyl and fused compounds containing 1,2-diamino groups can be used. All these combinations lead to condensed quinoxalines derivatives. In these cases the reaction conditions can be different, e.g., heating the reactants in refluxing EtOH solution (Michon et al. 2002; Elmes et al. 2011), refluxing in EtOH in the presence of catalytic amounts of *p*-TsOH (Unver et al. 2010), HCl (Kollenz and Theuer 2001), heating in AcOH solution at reflux (Shibinskaya et al. 2011), in an ionic liquid ([bmim] Br/MW) (Zare et al. 2010), stirring in EtOH solution at room temperature in the presence of catalytic amounts of TiO_2–P25–SO_4^{2-} (Krishnakumar and Swaminathan 2010), TiO_2–SO_4^{2-} (Krishnakumar et al. 2010), $NbCl_5$ (Hou et al. 2010), stirring in EtOH/H_2O solution at room temperature in the presence of catalytic amounts of silica-bonded S-sulfonic acid (Niknam et al. 2009) stirring in MeCN/H_2O solution at room temperature in the presence of catalytic amounts of Zn^{2+}-K10-clay (clayzic) (Dhakshinamoorthy et al. 2011), and stirring a CH_2Cl_2 solution at room temperature in the presence of catalytic amounts of ethereal HCl (Kollenz and Theuer 2001), in boiling pyridine (Kulisic et al. 2011) or toluene (Michon et al. 2002) solutions.

Not only the usual 1,2-DABs, but also 2,3,6,7,14,15-hexaammoniumtriptycene hexachloride **181**–compound containing three 1,2–DABs fragments–can contribute to the construction of quinoxaline systems (Mastalerz et al. 2011). The two-step synthesis of the ammonium salt **181** starts (Scheme 2.7) with a sixfold nitration of triptycene **179** (Shalaev and Skvarchenko 1974). Triptycene **179** was dissolved in fuming nitric acid and heated at 80–85 °C for 4 h giving after workup a pale yellow solid as crude product. From ^{1}H NMR spectroscopy it can be estimated that the desired hexanitrotriptycene **180** was formed as the main product in approximately a 38 % yield. By recrystallization from hot DMF it was possible to separate **180** as yellow needles from the crude mixture in yields between 16 and 18 % of sufficient purity (approximately 97 % of the desired regioisomer as quantified by ^{1}H NMR spectroscopy).

The reduction using tin(II) chloride in aqueous hydrochloride/ethanol solution was carried out for the subsequent sixfold transformation of the hexanitrotriptycene **180** to the corresponding hexaammonium hexachloride **181**. This resulted in the pale yellow ammonium salt **181** as a heptahydrate, which was determined by elemental analysis, in quantitative yield. This was found (Mastalerz et al. 2011) to be superior to methods using Pd/C and H_2 or Raney-Ni/hydrazine. The reaction was performed in air, and no precautions were found to be necessary. More important to us than the high yield is the stability of **181** toward oxidation, which was known before for similar structures (Far et al. 2002) containing electron-rich 1,2-DAB units. This stability makes the handling for further transformations easier, which is exemplified in some selected condensation reactions (Scheme 2.8). For example, with triethyl orthoformate the benzimidazole analog of triptycene **183a** is accessible in almost quantitative yield (98 %) (Far et al. 2002) by directly using the ammonium salt **181** as a reactant in water as solvent. Similarly, a benzotriazole analog **183b** is accessible in a 61 % yield by reacting **181** with sodium nitrite and potassium acetate at room temperature (Damshoder and Peterson 1940). Quinoxaline



Scheme 2.7 Two-step synthesis of air-stable hexaammoniumtriptycene hexachloride **181** as a synthetic analog of hexaminotriptycene **182**

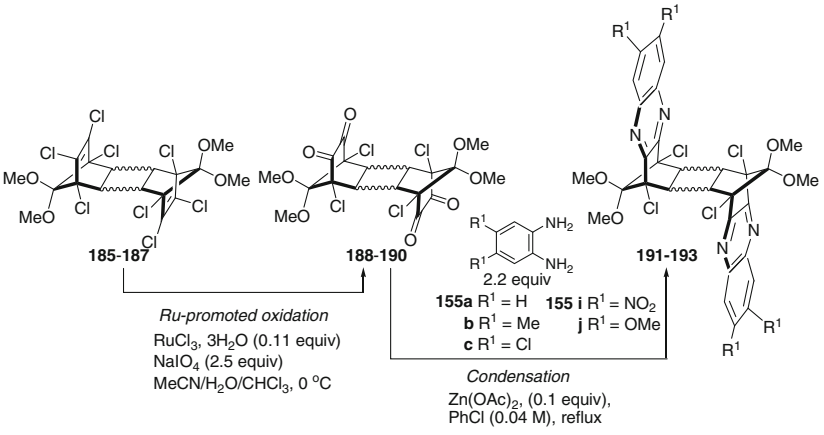


Scheme 2.8 Reactions of hexaammonium salt **181** in condensation reactions

derivative–2,3,6,7,12,13-hexahydroxy-2,6,12-trihydrotripty[2,3-d:6,7-d′:12,13-d″] tripyrazyl **184a** can be prepared by the reaction of the hexaammonium salt **181** with diethyloxalate in water at 100 °C, giving the product as a pale yellow solid in high yield (95 %). For the reaction of **181** with dihydroxydioxane or anisil to the corresponding quinoxalines 2,6,12-trihydrotripty[2,3-d:6,7-d′:12,13-d″]tripyrazyl **184b** and 2,3,6,7,12,13-hexa(4′-methoxyphenyl)-2,6,12-trihydrotripty-[2,3-d:6,7-d ′:12,13-d″]tripyrazyl **184c** the addition of a stoichiometric amounts of potassium acetate is crucial. Treatment under similar conditions without potassium acetate gave no reactions while with potassium acetate quinoxaline **184b** was accessible in 75 % and quinoxaline **184c** in almost quantitative yield (95 %).

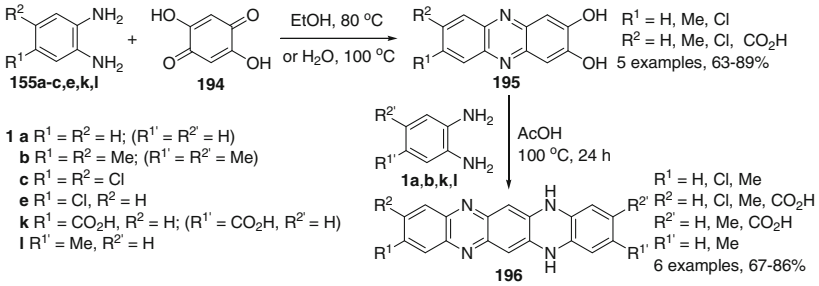
Compounds containing a two α-dicarbonyl fragments can act as a provider of two two-carbon fragments, e.g., reacting compounds **188–190** with 1,2-DAB derivatives **155a–c**, **i**, **g** gives Z-shaped quadruple-bridged orthocyclophanes **191–193** in one step (Scheme 2.9) (Chou and Liao 2011). Similarly, reaction of 2,5-dihydroxy-*p*-benzoquinone **194** in two stages makes it possible to synthesize unsymmetrically substituted 5,14-dihydro-5,7,12,14-tetraazapentacenes **196** (Scheme 2.10) (Seillan et al. 2008).

A three-step synthesis of nineteen Z-shaped quadruple-bridged [6,6] and [6,4] orthocyclophanes comprising two quinoxaline-based sidewalls has been described (Chou and Liao 2011). The synthesis began with the *bis*-Diels–Alder adducts



	Yields, %		
		188-190	**191-193**
	188,191	84	89-94
	189,192	95	92-94
	190,193	98	91-99

Scheme 2.9 Synthesis of quinoxaline-annelated Z-shaped quadruple-bridged orthocyclophanes **191–193**



Scheme 2.10 Synthesis of substituted 5,14-dihydro-5,7,12,14-tetraazapentacenes **196**

185–187 transformed by ruthenium-promoted oxidation into the *bis*-α-diketones **188–190**, which were then condensed with various 1,2-DABs **155a–e** to construct sidewalls (phane parts) of Z-shaped quadruple-bridged orthocyclophanes **191–193** (Scheme 2.9).

The commercially available 2,5-dihydroxy-*p*-benzoquinone **194** reacted with 1.1 equivalents of various substituted 1,2-DABs **155** to afford high yields of substituted 2,3-dihydroxyphenazines **195** (Yosioka and Otomasu 1954; Römer et al. 1979; Pozzo et al. 1998; Seillan et al. 2008). These could be reacted further over 24 h with an excess of substituted 1,2-DABs **155a**, **b**, **k**, **l** (10 equivalents) in the presence of glacial AcOH yielding pentacyclic derivatives **196** (Scheme 2.10) (Seillan et al. 2008).

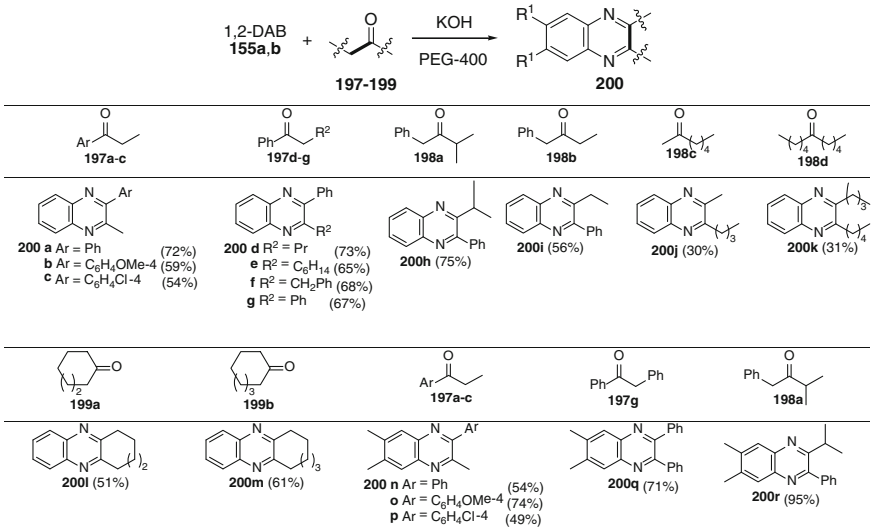
An efficient and practical route to a novel fluorescent benzo[*a*]pyrano[2,3-*c*] phenazine framework has been developed by a one-pot, four-component reaction of 2-hydroxynaphthalene-1,4-dione, 1,2-DABs, aromatic aldehydes, and Meldrum's acid in glacial acetic acid at 70 °C (Saluja et al. 2014).

Many of the dicarbonyl compounds required for this approach to quinoxalines are best obtained by oxidation of α-haloketones, α-ketoalcohols, or α-nitrosation or α-diazocoupling of ketones followed by the hydrolysis of the resulting monooximes or diazoketones. Therefore, under certain conditions, ketones such as α-haloketones, α-ketoalcohols, ketooximes, and diazoketones can be used directly for the synthesis of quinoxalines as suppliers of the two-carbon fragment.

2.2.3 With Ketones

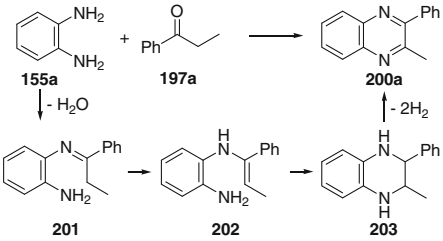
In air, 1,2-DABs **155a**, **b** react with an array of ketones **197–199** in PEG-400 at 60 °C in the presence of KOH to afford the corresponding quinoxalines **200** in good yields (Scheme 2.11) (Cho et al. 2007).

Although not fully understood as yet, a reaction pathway that is consistent with the product formed could proceed by the condensation ketone and diamine with the initial formation of a ketimine **201**. This in turn could tautomerize to form enamine **202**; KOH may play some role in facilitating this change. Subsequent steps may



Scheme 2.11 Ketones as two-carbon suppliers for quinoxaline synthesis

Scheme 2.12 A plausible reaction pathway for quinoxaline formation from a ketone and 1,2-DAB



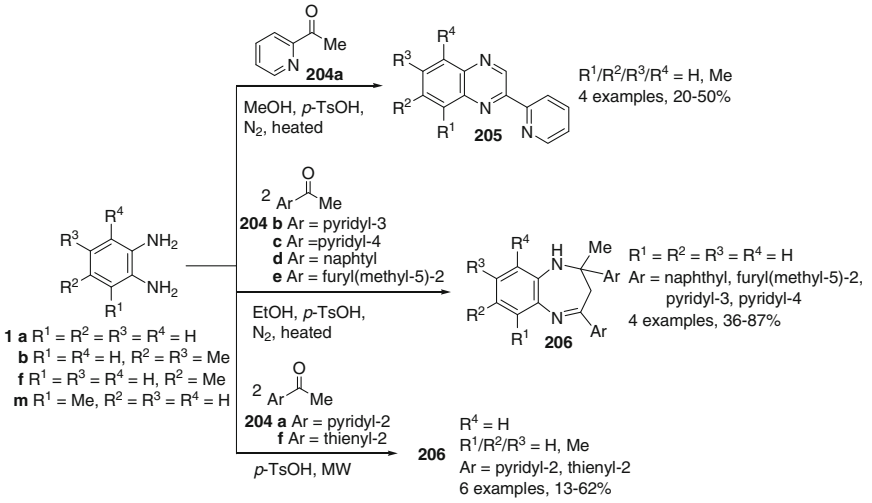
involve intramolecular hydroamination giving a 1,2,3,4-tetrahydroquinoxaline **203**, and then dehydrogenated to give **200a** (Scheme 2.12).

The reactions of **155a** with 1-arylpropan-1-ones **197b** and **197c**, which have either an electron-donating or an electron-withdrawing substituent on the aromatic ring, also proceed to give the corresponding 2-aryl-3-methylquinoxalines, **200b** and **200c**. Alkyl aryl ketones **197d–g** were also reacted with **155a** to give the corresponding 2-alkyl-3-arylquinoxalines **200d–g** in a yield range of 65–73 %. The reaction proceeds likewise with alkyl benzyl ketone **198a** to produce 2-isopropyl-3-phenylquinoxaline **200h**. However, the reaction did not proceed satisfactorily using acetophenone, with 2-phenylquinoxaline being formed in only a 20 % yield. In the reaction of **155a** with 1-phenylbutan-2-one **198b**, 2-ethyl-3-phenylquinoxaline **200i** was obtained in a 56 % yield with no formation of the regioisomer, 2-benzyl-3-methylquinoxaline. As shown in Scheme 2.12, the preferential formation of a 2-aryl-3-alkylquinoxaline seems to be due to the relative stability of the intermediate enamine. A lower reaction rate and yield were observed with nonactivated dialkyl ketones **198c** and **198d**. Here again, no regioisomeric

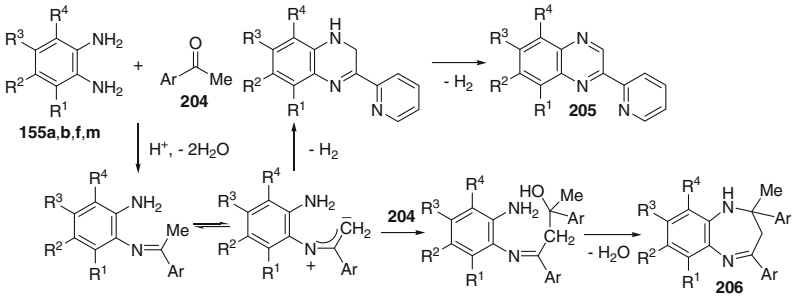
quinoxaline was observed with **198c**. Cyclic ketones such as cycloheptanone **199a** and cyclooctanone **199b** also reacted with **155a** to give 7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinoxaline **200l** and 6,7,8,9,10,11-hexahydrocycloocta[*b*]quinoxaline **200m** in 51 and 61 % yields, respectively. A similar treatment of **155b** with alkyl(aryl) ketones **197a–c** and **197g** afforded corresponding quinoxalines **200n–q** in the 49–74 % yield range. The cyclization of **155b** with **198a** resulted in a quantitative yield of quinoxaline **200r**.

It should be pointed out that in the presence of *p*-TsOH as a catalyst the reaction of 1,2-DABs **155a**, **b**, **f**, **m** with acetylarenes **204** in hot EtOH and under microwave irradiation conditions proceeds with the formation of 2,3-dihydro-1,5-benzodiazepine derivatives **206** in moderate yields (Scheme 2.13) (Yong et al. 2005). Unexpectedly, it was found that quinoxalines **205** are formed in the reaction of 1,2-DABs **155a**, **b**, **h**, **j** with 2-acetylpyridine **204a** in MeOH in contrast to 3- and 4-acetylpyridines **204b**, **c** and other acetylarenes **204d–f** derivatives (Scheme 2.13).

The alternative formation of quinoxalines **205** and benzodiazepines **206** can be understood with the help of the proposed reaction mechanism (Scheme 2.14). 1,2-DABs **155a**, **b**, **f**, **m** react with ketone **204** to form an imino-intermediate, which by *N*-protonation and C-deprotonation may form a zwitterion. In the case of the 2-substituted pyridine in MeOH solution, it is proposed that this intermediate cyclizes and is dehydrogenated to form quinoxaline derivatives **205**. The formation of quinoxaline derivatives is limited to those reactions in which the aryl group is 2-pyridyl and there still remains a question over the oxidation to the final product. When the zwitterionic intermediate reacts at carbon with another equivalent of the ketone, a new intermediate could be formed which could undergo further cyclisation to give benzodiazepine derivatives **206**.



Scheme 2.13 The synthesis of quinoxalines from methyl aryl/hetaryl ketones and 1,2-DABs



Scheme 2.14 Plausible mechanisms for formation of various benzo-fused heterocycles

β-Keto esters and β-diketones can also be used for quinoxaline synthesis instead of simple ketones. In these cases the key strategy is in situ preparation of α-halo-β-keto esters and α-halo-β-diketones by the reaction of *N*-bromosuccinimide, and then condensation with 1,2-DABs. This approach offers a simple, efficient, and mild synthesis of highly substituted quinoxalines in good yields (Kumar et al. 2001).

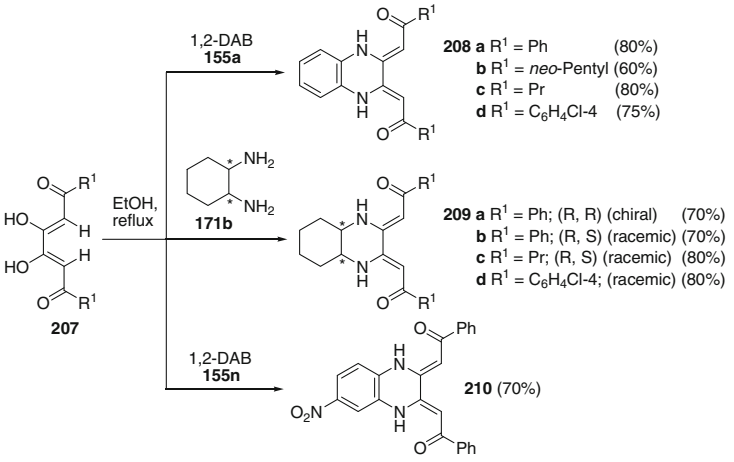
2.2.4 With Hexane-1,3,4,6-tetraones

Hexane-1,3,4,6-tetraones **207**, easily available from the double Claisen condensation of methyl ketones and diethyl oxalate (MeONa in ether) (Waring et al. 2002), react with 1,2-DABs **155a**, **n** and (*R*,*R*)-1,2-DACH **171b** in refluxing EtOH in the same way as α-diketones, resulting in symmetrically substituted quinoxalines **208**, **209** and a dissymmetrically substituted quinoxaline **210**, all bearing two ketonic arms (Scheme 2.15) (Waring et al. 2002).

On the basis of IR and ^{1}H NMR spectral data it was shown that of the three possible tautomeric forms (*bis-keto-imine*, *bis-enol-imine*, *bis-keto-enamine*), quinoxaline **208a** adopts the *bis-keto-enamine* form. Of the six possible tautomeric forms (every two of *keto-imine/keto-enamine, hydroxyl-ene-imine/keto-ene-amine*, *keto-enamine/enol-imine* forms) in quinoxaline **210** the *hydroxyl-ene-imine/keto-ene-amine* form is adopted (Waring et al. 2002). The structures of compounds **208a** and **210** were also confirmed by X-ray analysis and deduced from theoretical calculations of the possible limiting structures (Fig. 2.19) (Waring et al. 2002).

2.2.5 With Haloketones

As distinct from the reactions of dicarbonyl compounds, the reaction of α-halo ketones with 1,2-DABs proceeds with the formation of noncyclised products (Welton 1999; Wasserscheid and Keim 2000; Wilkes 2002; Zerth et al. 2003;



Scheme 2.15 Synthesis of quinoxaline derivatives **208–210**

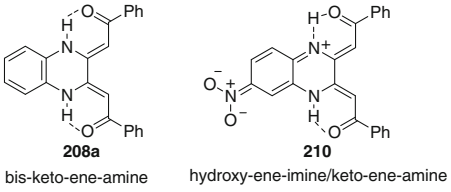
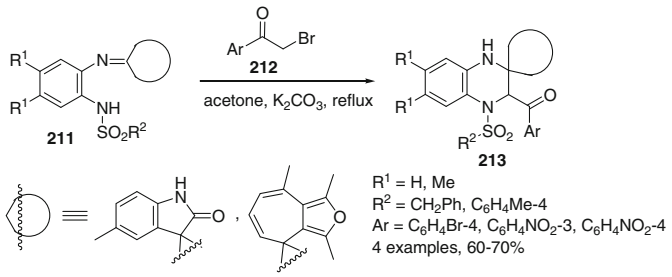


Fig. 2.19 Structures of compound **208a** and **210** as confirmed by X-ray crystallography and deduced from the theoretically limiting forms

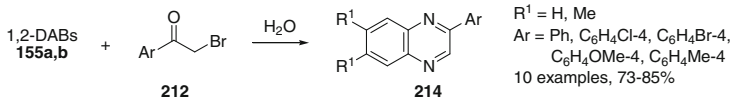
Kumar and Pawar 2004; Gu et al. 2005) formed by reaction with the carbonyl group only, or with dihydroquinoxaline derivatives (Das et al. 2007; Chou et al. 2011). Thus, these reactions are usually carried out in the presence of oxidants or under conditions that promote oxidation (Wu and Ede 2001; Singh et al. 2004; Das et al. 2007; Madhav et al. 2009; Meshram et al. 2010; Chou et al. 2011).

Alkylation of *o*-(*N*-sulfonylamino)phenyimino derivatives of indol-2-one and cyclohepta[*c*]furan **211** with phenacyl bromides **212** is accompanied by cyclization to tetrahydroquinoxalines **213** with spiro-fused oxoindole or cyclohepta[*c*]furan fragments (Scheme 2.16) (Kurbatov et al. 2004). In these cases, only one carbon atom is supplied by the phenacyl bromides for the construction of the pyrazine.

A catalyst-free and greener approach for the synthesis of quinoxalines from 1,2-DABs and phenacyl bromides via a one-pot oxidative cyclisation reaction in water has been described (Kumar et al. 2015). A typical experiment was performed by choosing 1,2-DAB **155a** (R = H) and phenacyl bromide **212a** (Ar = Ph) as model substrates to synthesize 2-phenylquinoxaline **214a** (Ar = Ph) (Scheme 2.17). With the advantages of using a greener solvent in mind, water was employed as the



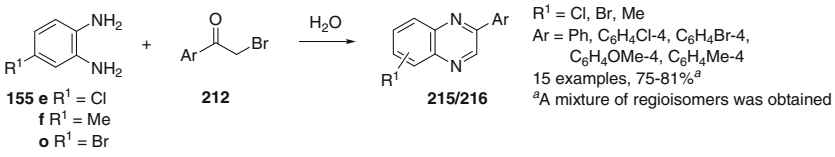
Scheme 2.16 The synthesis of spiro-quinoxalines **213**



Scheme 2.17 Reactions of symmetrical diamines with phenacyl bromides

medium for the reaction. However, at ambient temperature the reaction was found to be sluggish. To accelerate the reaction, dependence on temperature was examined at intervals of 20 °C over a range from 0 to 100 °C. As the temperature increased the yield of the product also increased affording a maximum yield of 85 % at 80 °C. To generalize the scope of the reaction, experiments were performed with various symmetrical diamines and substituted phenacyl bromides containing electron-withdrawing as well as electron-donating groups. Results are provided in Scheme 2.17. The reaction proceeded smoothly in all the cases illustrating that the presence of withdrawing/donating substituents on the aromatic ring of phenacyl bromide was well tolerated.

The reaction was further examined by employing unsymmetrical diamines **155e**, **f**, **o** (Scheme 2.18) which would afford the regioisomeric products **215/216** (Kumar et al. 2015). With electron-withdrawing substituents on the 1,2-DABs, two regioisomeric products with substituents at positions 6 and 7 were obtained in a ratio of 2:1, respectively. The isomers were separable by column chromatography using a mixture of EtOAc/Hexane. However, with electron-donating groups, an inseparable mixture of the regioisomers was obtained.



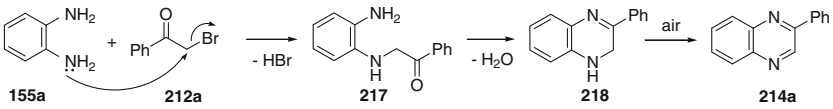
Scheme 2.18 Reactions of unsymmetrical diamines with phenacyl bromides

A plausible reaction mechanism for the formation of quinoxaline derivatives from 1,2-DAB and phenacyl bromide is illustrated in Scheme 2.19. Initially, a nucleophilic substitution occurs on the phenacyl bromide to afford the intermediate **217**. Intermediate **217** spontaneously cyclises to form 3-phenyl-1,2-dihydroquinoxaline **218**, which undergoes aromatization under air oxidation to afford 2-phenylquinoxaline **214a** as the final product.

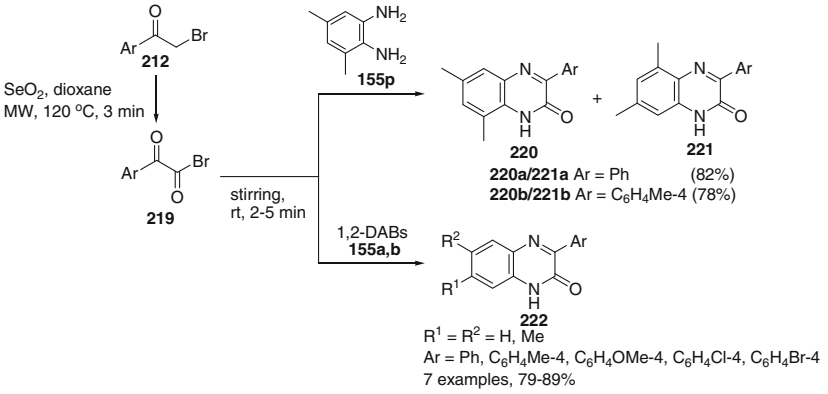
α-Bromoketones **212** undergo selenium dioxide oxidation to yield reactive 2-oxo-2-arylacetyl bromides **219** that are trapped by 1,2-DABs **155a**, **b**, **p**, to give quinoxalinones **220**–**222**, in good yield (Nagaraj et al. 2013) (Scheme 2.20).

It should be noted that the reaction route and the structure of products formed from compounds containing both diketone and α-halocarbonyl fragments depend on the solvent. For example, the reaction of 3-chloro-1,3-diphenylpropane-1,2-dione **223** with 1,2-DAB **155a** in acetic acid involves the α-diketone fragment and produces quinoxaline **224**; however, in MeONa in MeOH, the reaction involves the α-chloro ketone fragment to give 1,2-dihydroquinoxaline **225** (Scheme 2.21) (Mamedov et al. 1991).

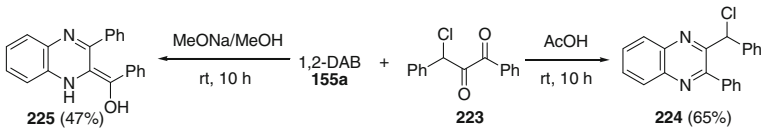
The reactions of 1,2-DAB **155a** with 3-aryl- and 3-alkyl-3-chloropyruvate esters **156e** afford quinoxalin-2-(1*H*)-ones **226** (Scheme 2.22) (Mamedov et al. 1989, 2010; Saifina et al. 2009). In this case, the formation of the quinoxaline ring involves the α-keto group of the ester rather than the α-chloro ketone fragment.



Scheme 2.19 Plausible reaction mechanism

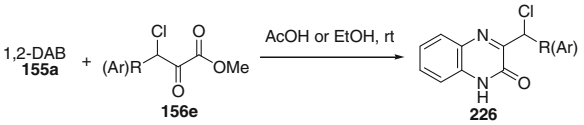


Scheme 2.20 Synthesis of quinoxalinones from 2-oxo-2-aryl acetyl bromides **219**



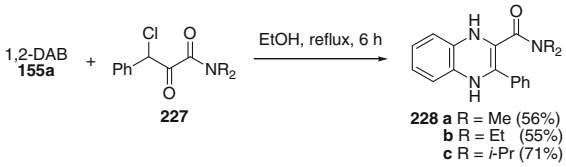
Scheme 2.21 The reaction of 3-chloro-1,3-diphenylpropane-1,2-dione **223** with 1,2-DAB **155a** under various conditions

Scheme 2.22 The synthesis of 3-(α-chloroalkyl) quinoxalin-2(1*H*)-ones **226**

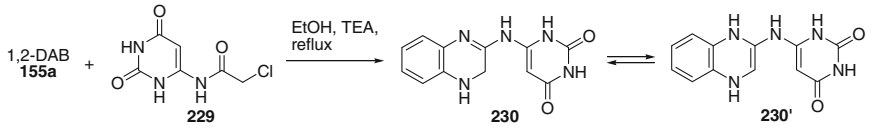


In the case of 3-chloro-3-phenylpyruvamides **227**, reaction with 1,2-DAB **155a** involves the α-chloro ketone fragment, giving rise to 1,4-dihydroquinoxalines **228**. These are due to the relatively easy alkylation of the amino group, unlike the transamidation of the amide group (Scheme 2.23) (Mamedov et al. 1989).

As distinct from 3-chloro-3-phenylpyruvamides **227,** 6-chloroacetylaminouracil **229** was refluxed with 1,2-DAB in the presence of triethyl amine (Bondock et al. 2011) to yield dihydroquinoxalin-2-ylamino derivative **230** as a mixture of quinoxalinyl-C(3)–CH_2- and quinoxalinyl-C(3)=CH- tautomers (Sarg and El-Shaer 2014) (Scheme 2.24).



Scheme 2.23 The synthesis of 2-*N*,*N*-dialkylcarbamoyl-3-phenyl-1,2,3,4-tetrahydroquinoxalines **228**



Scheme 2.24 The reaction of 6-chloroacetylaminouracil with 1,2-DAB in the presence of TEA

2.2.6 With α-Hydroxy Ketones

A general and practical route for the synthesis of 2-substituted quinoxalines using HgI_2 as a catalyst has been reported (Kotharkar and Shinde 2006). In the presence of mercuric iodide (HgI_2), the reaction of hydroxyl ketone and 1,2-DAB was carried out in a one-pot condition at 60 °C and resulted in the formation of quinoxaline in 60–85 % yield (Table 2.1). Many pharmacologically relevant substituents on the aromatic ring could be introduced with high efficiency in moderate to excellent yields with high purities.

2-Substituted quinoxalines can be also prepared by a one-pot process commencing from hydroxy ketones using a MnO_2 (Raw et al. 2004), $FeCl_3$/morpholine (Song et al. 2012), and silica gel (Jeena and Robinson 2014)–mediated tandem oxidation process (Table 2.1).

2.2.7 With Vicinal Diols

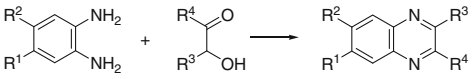
In the presence of a catalytic amount of a ruthenium catalyst, 1,2-DABs **155a**, **b** react with an array of vicinal diols **233** in diglyme with KOH to afford the corresponding quinoxalines **234** in good yields (Scheme 2.25) (Cho and Oh 2006).

2.2.8 With Dimethyl (DMAD) and Diethyl (DEAD) Acetylenedicarboxylates

A fast and efficient method which is associated with the use of dialkyl acetylenedicarboxylates and 1,2-DAB, mild conditions, producing excellent yields, was established for the synthesis of quinoxalin-2(1*H*)-ones in water under catalyst-free conditions. The reactions of 1,2-DAB **155a** and naphthalene-2,3-diamine (2,3-DAN) **235** with DMAD **236a** and DEAD **236b** were carried at 50 °C to provide corresponding 3-(alkoxycarbonylmethylene)-quinoxalin(benzoquinoxalin)-2(1*H*)-ones **238a**, **b** and **239a**, **b** in 92–96 % yields (Scheme 2.26). When the aromatic ring in the substrate is replaced by an aliphatic ring 1,2-DACH **171a**, product is formed in a 91 % yield (Zhang et al. 2008). It should be pointed out that under microwave irradiation the rapid addition of DMAD **236a** and DEAD **236b** to 1,2-DAB **155a** in a solventless system also afforded quinoxalin-2(1*H*)-ones **239a**, **b** in 90 and 85 % yields (Heravi et al. 2005).

When divinyl fumarate **237** was used in the reactions with 1,2-DAB **155a** and 1,2-DAN **235** in water at 50 °C, the processes proceeded smoothly and afforded the corresponding vinyloxycarbonyl methyl 3,4-dihydroquinoxalin(benzoquinoxalin)-2(1*H*)-ones **238c**, **239c** in good yields (Scheme 2.26) (Zhang et al. 2008).

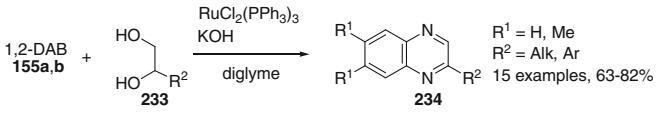
Table 2.1 One-pot synthesis substituted quinoxalines from hydroxy ketones



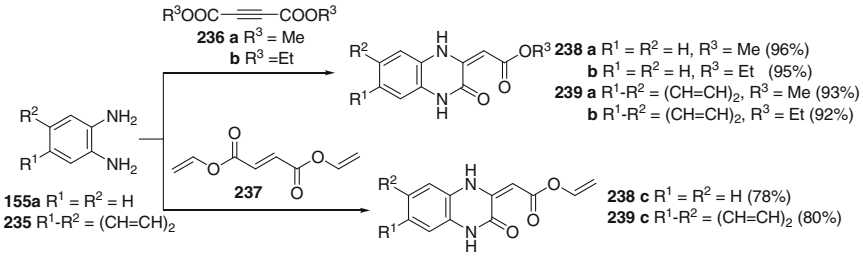
155a,b,e,f,n **231** **232**

Entry	**232**	R^1	R^2	R^3	R^4	Yield (%) with the use			
						HgI_2	MnO_2	$FeCl_3$/morph	Silica gel
1	**232a**	H	H	Ph	Ph	85	75	95	34[a] 77[b]
2	**232b**	H	H	H	Ph	80	79	–	38[a] 81[b]
3	**232c**	H	H	H	Me	80	79	–	31[a] 85[b]
4	**232d**	H	H	H	furanyl-2	80	89	–	–
5	**232e**	H	H	H	*c*-Hexyl	85	78	–	–
6	**232f**	Me	Me	H	Ph	75	66	–	29[a] 89[b]
7	**232g**	Me	Me	H	*c*-Hexyl	80	89	–	–
8	**232h**	Me	Me	H	$(CH_2)_4Me$	60	62	–	–
9	**232i**	H	H	H	C_6H_3-di-Cl-2,4	75	–	–	–
10	**232j**	H	H	H	C_6H_4Cl-4	80	–	–	–
11	**232k**	H	H	H	C_6H_4F-4	82	–	–	–
12	**232l**	Me	Me	H	C_6H_3-di-Cl-2,4	83	–	–	–
16	**232m**	H	H	H	C_6H_3-di-F-2,4	83	–	–	–
17	**232n**	Me	Me	Ph	Ph	–	–	–	41[a] 70[b]
18	**232o**	Cl	H	Ph	Ph	–	–	–	31[a] 73[b]
19	**232p**	H	H	C_6H_4Me-4	C_6H_4Me-4	–	–	95	–
20	**232q**	H	H	C_6H_3-di-Cl-2,4	C_6H_3-di-Cl-2,4	–	–	94	–
21	**232r**	H	H	C_6H_4OMe-4	C_6H_4OMe-4	–	–	96	–
22	**232s**	H	H	furanyl-2	furanyl-2	–	–	93	–
23	**232t**	H	H	Me	Me	–	–	72	–
24	**232u**	NO_2	H	Ph	Ph	–	–	90	–
25	**232v**	NO_2	H	furanyl-2	furanyl-2	–	–	90	–
26	**232w**	NO_2	H	Me	Me	–	–	65	–
27	**232x**	Me	H	Ph	Ph	–	–	96	–
28	**232y**	Me	H	furanyl-2	furanyl-2	–	–	94	–
29	**232z**	Me	H	Me	Me	–	–	77	–

[a]Microwave conditions open vessel
[b]Microwave conditions closed vessel

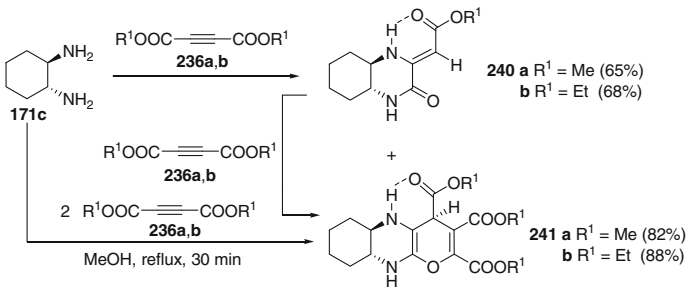


Scheme 2.25 A ruthenium-catalyzed approach for quinoxalines **234** from 1,2-DABs **155a**, **b** and vicinal diols **233**



Scheme 2.26 The reactions of 1,2-DAB **155a** and 1,2-DAN **235** with DMAD **236a**, DEAD **236b** and divinyl fumarate **237** in water

The use of *trans*-(1*R*,2*R*)-1,2-diaminocyclohexane (*trans*-(1*R*,2*R*)-1,2-DACH) **171c** instead of 1,2-DACH **171a** in the reactions with DMAD **236a** and DEAD **236b** was carried out at reflux in MeOH which provided 3-(alkoxycarbonylmethylene)-3,4,4a*R*,5,6,7,8,8a*R*-octahydroquinoxalin-2(1*H*)-ones **240a**, **b** (Scheme 2.27) (Nami et al. 2008). The reaction of compounds **240a**, **b** with dialkyl acetylenedicarboxylate (1:1) or the reaction of *trans*-(1*R*,2*R*)-1,2-DACH **171c** with dialkyl acetylenedicarboxylate (1:2) resulted in trialkyl 4*S*,5a*R*,9a*R*-4*H*-pyrano[2,3-*b*]-5,5a,6,7,8,9,9a,10-octahydroquinoxaline-2,3,4-tricarboxylates **241a**, **b** (Scheme 2.27) (Nami et al. 2008).



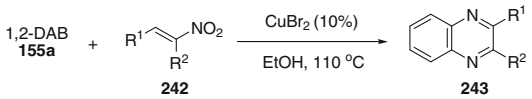
Scheme 2.27 The reaction of *trans*-(1*R*,2*R*)-1,2-DACH **171c** with DMAD **236a** and DEAD **236b** in ratios of 1:1 and 1:2

2.2.9 With Nitroolefins

An easy and efficient copper-catalyzed reaction for the synthesis of quinoxalines from 1,2-DABs and nitroolefins has been developed (Chen et al. 2013). This reaction could proceed well enough without any additional base and be applied to various available substrates with a one-step synthetic procedure in moderate to good yields.

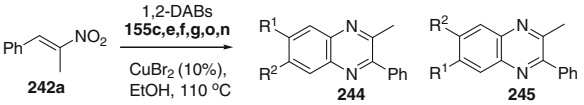
A series of nitroolefins **242** were investigated to establish the scope and limitations of this process. A wide range of substituted groups of nitroolefins gave the desired products in moderate to good yields, which include methyl, methoxyl, hydroxyl, chloro, cyano groups, etc. (Table 2.2). The electron-rich nitroolefins showed better reactivities and gave higher yields than the electron-deficient ones. Substitution at 2-position of nitroolefins had a significant impact on yields and resulted in lower yields (entries 10–13, 15). However, substitution at 3-position of nitroolefins had only a slight impact on yield (entry 14). Besides, (E)-2-(2-nitrovinyl)furan failed to afford the desired reaction (entry 16). Because of the instability of the substrate (entry 17), (E)-(2-nitrovinyl)benzene probably gave a lower yield in DMSO.

Table 2.2 Reactions of various nitroolefins **242** with 1,2-DAB **155a**



Entry	**242**	R^1	R^2	**243**	Yield (%)
1	**242a**	Ph	Me	**243a**	90
2	**242b**	C_6H_4Me-4	Me	**243b**	77
3	**242c**	C_6H_4OMe-4	Me	**243c**	80
4	**242d**	C_6H_4OH-4	Me	**243d**	86
5	**242e**	C_6H_4Cl-4	Me	**243e**	77
6	**242f**	C_6H_4Br-4	Me	**243f**	81
7	**242g**	$C_6H_4NO_2$-4	Me	**243g**	62
8	**242h**	C_6H_4CN-4	Me	**243h**	64
9	**242i**	$C_6H_4CF_3$-4	Me	**243i**	71
10	**242j**	C_6H_4OMe-2	Me	**243j**	35
11	**242k**	C_6H_4Cl-2	Me	**243k**	42
12	**242l**	C_6H_4Br-2	Me	**243l**	42
13	**242m**	$C_6H_4NO_2$-4	Me	**243m**	38
14	**242n**	C_6H_4Cl-3	Me	**243n**	63
15	**242o**	C_6H_3-di-Cl-2,4	Me	**243o**	45
16	**242p**	furanyl-2	Me	**243p**	0
17	**242q**	Ph	H	**243q**	40

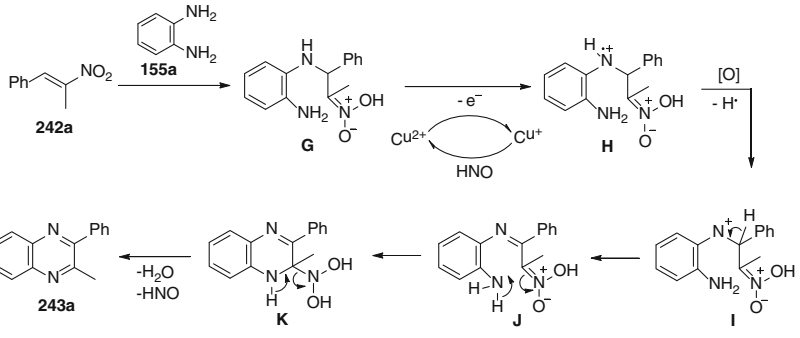
Scheme 2.28 Reactions of (*E*)-(2-nitroprop-1-en-1-yl) benzene **242a** with substituted 1,2-DABs **155**



244a/245a R^1 = Me, R^2 = H (65%)
244b/245b R^1 = OMe, R^2 = H (53%)
244c/245c R^1 = Cl, R^2 = H (86%)
244d/245d R^1 = Br, R^2 = H (89%)
244e/245e R^1 = NO_2, R^2 = H (61%)
244f R^1 = R^2 = Cl (93%)

The reaction scope was also investigated with respect to the other coupling partner **155** (Scheme 2.28). Generally, most of the substrates provided moderate to good yields. Higher yields were obtained with electron-withdrawing substituents on the aromatic ring. It should be pointed out that in this transformation poor regioselectivities were observed. The ratio of isomers **244a–e/245a–e** varied from 1.1:1 to 2.1:1, confirmed by NMR. Unfortunately, coupling of (E)-(2-nitroprop-1-en-1-yl)benzene **242a** with 1,2-diaminoanthracene-9,10-dione and 1,2-cyclohexanediamine did not take place using a similar procedure, probably because of the electronic effect of 1,2-diaminoanthracene-9,10-dione and the configuration of 1,2-cyclohexanediamine.

To gain an insight into the mechanism of the above-mentioned process, the following control experiment was performed. **243a** was also obtained in a 88 % yield via the reaction of **242a** with **155a** under N_2-protected conditions. Thus, it was considered the NO_2 group to be the terminal oxidant in this process. Based on the above results, a tentative reaction mechanism has been illustrated in Scheme 2.29. The substrate **242a** initially reacts with **155a** to produce the Michael addition intermediate **G**, which can be a one-electron oxidized by copper(II) to form the radical cation **H**. Beside, **I** is generated from **H** through hydrogen abstraction with oxidation, and then **J** is formed by proton elimination (Li 2009; Yan et al. 2012). Finally, the proton transfer and intramolecular cyclization followed by elimination of H_2O and HNO from the intermediate **K** resulted in the desired product **243a** (Shiraishi et al. 1998; Maiti et al. 2010; Kundu et al. 2011).

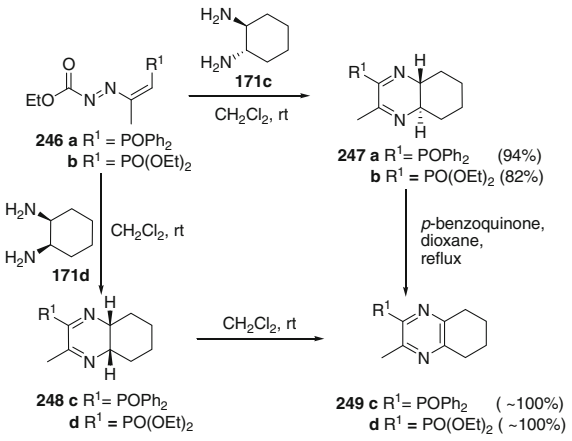


Scheme 2.29 Proposed mechanism

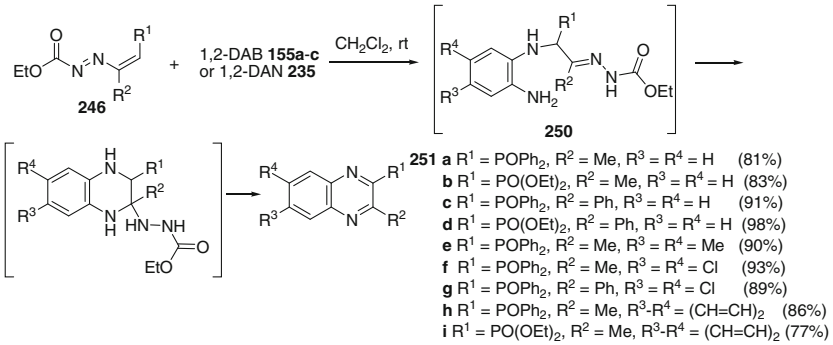
2.2.10 With 1,2-Diaza-1,3-butadienes

The Michael addition of (±)-*trans*-1,2-DACH **171c** to the heterodiene system of 1,2-diaza-1,3-butadiene **246a** in CH_2Cl_2 at room temperature gave rise stereoselectively to the formation of *trans*-4a,5,6,7,8,8a-hexahydroquinoxalinehydro-2-phosphine oxide **247a** in a 94 % yield. The reaction of 1,2-diaza-1,3-butadiene **246b** with (±)-*trans*-1,2-DACH **171c** provided **247b** in good yield. The aromatization of **247a** was performed under reflux by oxidation with *p*-benzoquinone in 1,4-dioxane resulting in 5,6,7,8-tetrahydroquinoxaline-2-phosphine oxide **249c**. Under similar conditions, the oxidation of **247b** did not lead to 2-phosphonylpyrazine **249**, but only to decomposition products. The reaction of 1,2-diaza-1,3-butadienes **246a**, **b** with (±)-*cis*-1,2-DACH **171d** gave rise to *cis*-4a,5,6,7,8,8a-hexahydroquinoxalines **248c**, **d**. In this case, oxidation readily occurred in the reaction media (air atmosphere), and pyrazine **249c** was easily obtained from dihydropyrazine **248c**. However, it was impossible to isolate tetrahydroquinoxaline **249d**, even though its presence in the reaction mixture, together with the **248d**, was confirmed by ^{1}H and ^{31}P NMR spectroscopy (Scheme 2.30) (Aparicio et al. 2006).

1,2-Diaza-1,3-butadienes containing a carboxylate group at the terminal carbon have been used as starting materials for the preparation of quinoxaline-2-carboxylates (Attanasi et al. 2001, 2003). The addition of 1,2-DAB **155a** to the heterodiene system of **246a** led to the formation of quinoxaline-2-phosphine oxide **251a** in an 81 % yield (Scheme 2.31) (Aparicio et al. 2006). The first step of the reaction is the nucleophilic attack of an amino group of 1,2-DAB **155a–c** and 2,3-DAN **235** on the terminal carbon of the heterodiene system of 1,2-diaza-1,3-butadienes **246** with the formation of the hydrazone 1,4-adduct (Michael type) **250**. The subsequent nucleophilic attack of the second amino group at the hydrazone carbon with the loss of a hydrazine carboxylate residue results in 2-phosphorylated quinoxalines **251a–i**. This strategy affords a very efficient entry to quinoxaline phosphine oxides **251a**, **c**, **e–h** and phosphonates **251b**,



Scheme 2.30 The Michael addition of ((±)-*trans*-(and *cis*))-1,2-DACH **171c**,**171d** to the heterodiene system of 1,2-diaza-1,3-butadiene **246**



Scheme 2.31 The synthesis of phosphorylated quinoxalines

d, **i** (Scheme 2.31) (Aparicio et al. 2006). Quinoxalines directly substituted with phosphorus-containing functional groups have received scarce attention (Ito et al. 1996; Acklin et al. 1998; Sinou et al. 2004; Imamoto et al. 2005). This appears to be the first synthesis of quinoxalines with a phosphonate group.

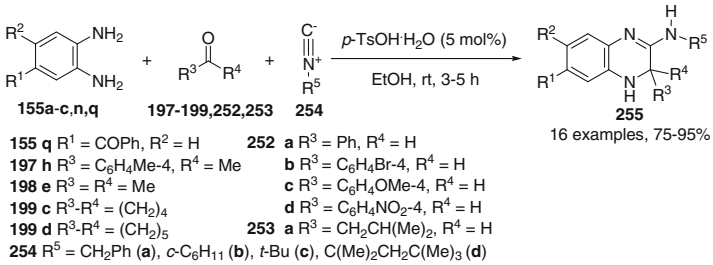
2.2.11 With Ketones(Aldehydes) and Isocyanide

Multicomponent reactions (MCRs) have become important tools in modern preparative synthetic chemistry because they increase efficiency by combining several operational steps without the isolation of intermediates or changing the reaction conditions (Litvinov 2003; Zhu and Bienayme 2005). MCRs have emerged as valuable tools for the preparation of structurally diverse chemical libraries of drug-like heterocyclic compounds (Ugi et al. 1994, 2000; Tietze and Modi 2000). Isocyanide-based MCRs are especially important in this area (Dömling and Ugi 2000; Dömling 2006).

In 2008, Shaabani and coworkers reported an elegant and hitherto unknown reaction that affords 3,4-dihydroquinoxalin-2-amines **255** via the three-component condensation of 1,2-DAB **155a–c**, **n**, **q** and ketones **197–199** or aldehydes **252**, **253**, and an isocyanide **254** in the presence of a catalytic amount of *p*-TsOH·H_2O in EtOH at room temperature in good to excellent yields (Scheme 2.32).

Shaabani and coworkers simply used 1,2-DAB or 1,2-DACH instead of heterocyclic systems containing a H_2N–C = N fragment in the known Groebke–Blackburn–Bienayme MCR reaction (Groebke et al. 1998; Blackburn et al. 1998; Bienayme and Bouzid 1998) (Ugi-type MCR reaction).

To explore the scope and limitations of this reaction, the procedure was extended to various alkyl, benzyl, and alicyclic isocyanides and aliphatic, alicyclic, and aromatic ketones, aliphatic and aromatic aldehydes with electron-withdrawing and electron-releasing groups at their *para* positions in aromatic diamines. The reaction



Scheme 2.32 Synthesis of 3,4-dihydroquinoxalin-2-amines **255** from the MCRs of various diamines **155**, ketones **197**–**199** or aldehydes **252**, **253**, and isocyanides **254**

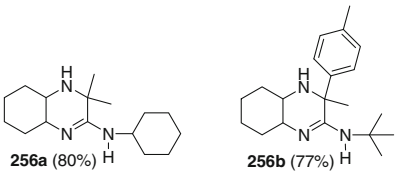


Fig. 2.20 Octahydroquinoxalines **256a**, **b**, produced from the MCRs of 1,2-DACH **171a**, ketones **197h**, **198e**, and isocyanides **254b**, **c**

proceeded very efficiently in excellent yields with the formation of the corresponding 3,4-dihydroquinoxalin-2-amine derivatives **255** (Scheme 2.32).

The amine component of the MCR is also variable. To examine the replacement of the aromatic diamine **155** (Scheme 2.32) with alicyclic 1,2-diamines, 1,2-DACH **171a** was used as an alicyclic diamine. The isolated products *N*-cyclohexyl-3,4,4*a*,5,6,7,8,8*a*-octahydro-3,3-dimethylquinoxalin-2-amine **256a** and *N*-*tert*-butyl-3,4,4*a*,5,6,7,8,8*a*-octahydro-3-methyl-3-*p*-tolylquinoxalin-2-amine **256b** were obtained in high yields (Fig. 2.20).

The reaction proceeds under mild conditions and is compatible with a wide range of functional groups. It is noteworthy that five substituents in the products (R^1–R^5) can be varied independently of each other.

It might be well to point out that after the initial paper (Shaabani et al. 2008), very simple, efficient, clean, and practical methods for the synthesis of highly substituted quinoxalin-2-amine derivatives in good yields have been reported. They proceed in the presence of HCl (33–54 %) (Krasavin and Parchinsky 2008; Krasavin et al. 2009), ferric perchlorate (91–93 %) (Heravi et al. 2009), cerium(IV) ammonium nitrate (CAN) (71–96 %) (Li et al. 2009a), and ethylenediaminetetraacetic acid (72–95 %) (Kolla and Lee 2010) as efficient catalysts correspondingly in MeOH, MeCN, EtOH, or H_2O.

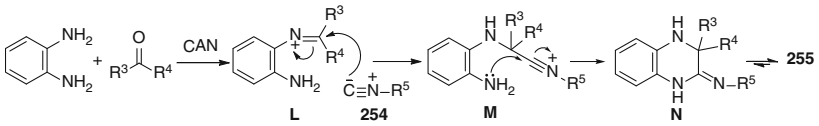
The mechanism has not been unequivocally established, but a possible one is outlined in Scheme 2.26. First, the carbonyl group could be activated by the

coordination of the oxygen atom with the catalyst. Thus the formation of iminium cation **L** could be facilitated (Varala et al. 2006). Nucleophilic addition of isocyanide **254** (Dömling and Ugi 2000) followed by an intramolecular cyclization of **M** could result in the generation of **N**, which would then be isomerized to the final product **255** (Scheme 2.33).

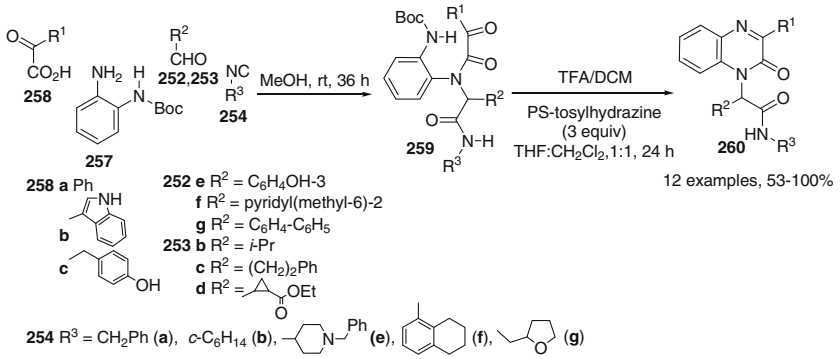
Although Ce(IV) derivatives are generally employed as single-electron transfer (SET) oxidants, the authors (Li et al. 2009a) believe that CAN serves as a Lewis acid in the above process in the same way as in other carbon–carbon and carbon–heteroatom bond-forming reactions (Nair et al. 2004a).

Simply mixing a mono-*N*-Boc protected 1,2-DAB **257**, glyoxylic acid **258**, isonitrile **254,** and aldehydes **252**, **253**, in methanol, gave the Ugi products **259**. TFA-promoted Boc removal and cyclization, with concomitant loss of water, afforded the desired quinoxalinone, with four potential points of diversity and of general structure, **260** (Scheme 2.34) (Nixey et al. 2002). This transformation represents a novel extension of the UDC (Ugi/de-Boc/cyclize) methodology for synthesizing 1,4-benzodiazepine-2,5-diones (Hulme et al. 1998).

For the use of the heterocyclic systems as providers of a two-carbon fragment in the synthesis of quinoxalines see Sect. 2.6.



Scheme 2.33 Proposed mechanism for the synthesis of products **255**

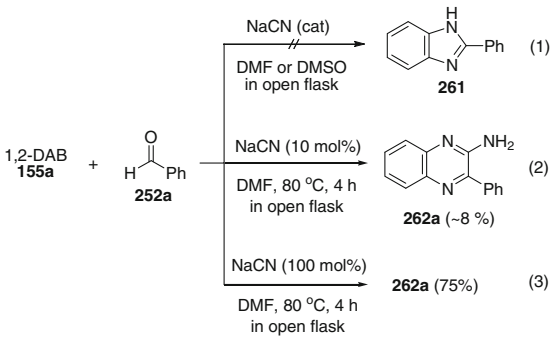


Scheme 2.34 Two-step solution-phase synthesis of novel quinoxalin-2(1*H*)-ones **260** utilizing a UDC (Ugi/de-Boc/cyclize) strategy

2.2.12 With Aldehydes and NaCN

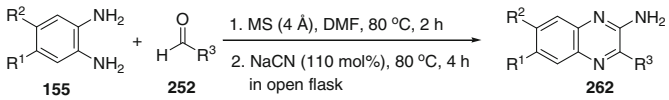
However, when 1,2-DAB **155a** and benzaldehyde **252a** were subjected to the oxidative cyclization conditions (Cho et al. 2012, 2013) used for benzoxazole and benzothiazole synthesis in the presence of a catalytic amount of NaCN, the expected benzimidazole **261** was not obtained (Scheme 2.35, Eq. 1). Instead, the corresponding imine was obtained as the major product along with an unexpected product in a slightly lower yield than the amount of NaCN used (Scheme 2.35, Eq. 2). When a stoichiometric amount of NaCN was used under the same conditions, the unexpected 3-phenyl 2-aminoquinoxaline **262a** was obtained as the major product (Scheme 2.35, Eq. 3) (Cho et al. 2014).

The substrate scope for this transformation was investigated (Table 2.3). Various aromatic aldehydes were employed according to this protocol. The electronic properties of the aromatic aldehydes had little effect on the synthesis of **262**; the desired products were obtained in high yields regardless of the electronic nature of the aromatic rings (entries 1–5). Benzaldehyde derivatives bearing a substituent at the *ortho*-position also provided the quinoxaline products in good to excellent yields (entries 6–8). In addition to benzaldehyde derivatives, fused aromatic aldehydes were also applied according to this protocol, and the desired products were obtained in high yields (entries 9 and 10). This transformation extended to heteroaromatic aldehydes, and the corresponding quinoxalines were obtained in good to high yields depending on the nature of the heteroaromatic ring system (entries 11–13). The authors then attempted to extend the method to more challenging aliphatic substrates. The subsequent addition of NaCN to imines generated from aliphatic aldehydes along with several side products provided the desired 2-aminoquinoxalines in moderate yields. However, when **155a**, an aliphatic aldehyde, and NaCN were added together and stirred at 80 °C, the three desired products were obtained in good yields (entries 14–16). Besides, the effect of substituents in ortho-phenylenediamines was evaluated on this transformation (entries 17–20). The electronic effect of substituents in 1,2-DABs had some influence on the formation of **262**. Electron-rich 1,2-DABs afforded the desired products in high yield (entries 17 and 19), whereas the 1,2-DABs bearing electron-withdrawing



Scheme 2.35 Formation of 2-aminoquinoxaline **262a**

Table 2.3 Substrate scope

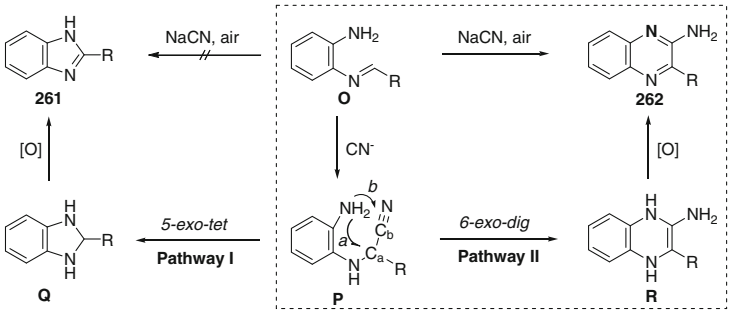


Entry	**155**	R^1	R^2	**252**	R^3	**262**	Yield (%)
1	**155a**	H	H	**252a**	Ph	**262a**	86
2	**155a**	H	H	**252b**	C_6H_4OMe-4	**262b**	80
3	**155a**	H	H	**252c**	C_6H_4Me-4	**262c**	77
4	**155a**	H	H	**252d**	C_6H_4Cl-4	**262d**	93
5	**155a**	H	H	**252e**	$C_6H_4CO_2Me$-4	**262e**	92
6	**155a**	H	H	**252f**	C_6H_4OMe-2	**262f**	92
7	**155a**	H	H	**252g**	C_6H_4Cl-2	**262g**	82
8	**155a**	H	H	**252h**	C_6H_4OH-2	**262h**	67
9	**155a**	H	H	**252i**	naphthyl-1	**262i**	73
10	**155a**	H	H	**252j**	naphthyl-2	**262j**	90
11	**155a**	H	H	**252k**	furanyl-2	**262k**	90
12	**155a**	H	H	**252l**	thienyl-2	**262l**	64
13	**155a**	H	H	**252m**	pyridyl-2	**262m**	64
14	**155a**	H	H	**252n**	*n*-Hexyl	**262n**	65
15	**155a**	H	H	**252o**	*c*-Hexyl	**262o**	60
16	**155a**	H	H	**252p**	*t*-Butyl	**262p**	70
17	**155b**	Me	Me	**252a**	Ph	**262q**	85
18	**155c**	Cl	Cl	**252a**	Ph	**262r**	60
19	**155f**	Me	H	**252a**	Ph	**262s**	88 (2:1)[a]
20	**155e**	Cl	H	**252a**	Ph	**262t**	72 (2:1)[b]

[a]Two regioisomers were obtained as an inseparable mixture in a 2:1 ratio
[b]Two separable regioisomers were obtained in 48 and 24 % yield, respectively

substituents showed much lower reactivities than the electron-rich 1,2-DABs and still yielded the desired products in good yields (entries 18 and 20).

The proposed mechanism of the reaction involves the following processes (Scheme 2.36). Cyanide undergoes nucleophilic addition to imine **O** to afford intermediate **P**. The resulting intermediate **P** can undergo two possible reaction pathways. The lone pair on the nitrogen atom can attack the sp^3-hybridized carbon atom (C_a in intermediate **P**) via *5-exo-tet* cyclization to yield benzimidazoline **Q**. The subsequent aerobic oxidation of **Q** would provide benzimidazole **261** (*Pathway I*). On the other hand, the nitrogen atom can attack the sp-hybridized carbon (C_b in intermediate **P**) of the nitrile via 6-exo-dig cyclization to furnish 2-amino dihydroquinoxaline **R**. A similar 6-exo-dig cyclization (*Pathway II*) has been already proposed in the literature without considering *5-endo-trig* cyclization (route *a*) (Shepherd and Smith 1987; Schwerkoske et al. 2005; Montagne and Shipman 2006; Polyakov et al. 2009; Haddadin et al. 2011; Guchhait et al. 2012).



Scheme 2.36 Possible reaction pathways

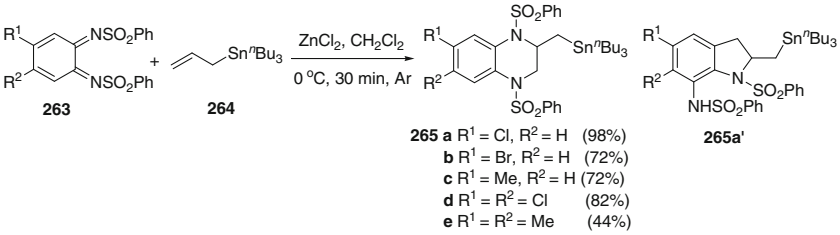
The desired 2-aminoquinoxaline **262** could be obtained after the aerobic oxidation of **R** (*Pathway II*). Under these conditions, 6-*exo-dig* cyclization would predominantly take place over 5-*exo-tet* cyclization presumably due to a better orbital orientation between HOMO and LUMO, which led to the exclusive formation of 2-aminoquinoxalines **262**. Although this transformation was previously reported in literature (Ricciardi and Joullie 1986; Hu et al. 2010), it should be noted that this transformation is operationally very simple and displayed a very broad substrate scope from aromatic aldehydes, heteroaromatic aldehydes, to more challenging aliphatic aldehydes.

2.3 Condensation of *o*-Benzoquinone Diimines and Diimides with Various Two-Carbon Unit Suppliers

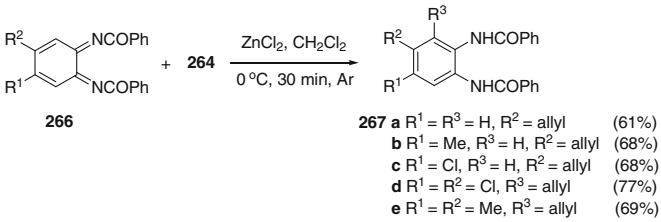
2.3.1 With Allylstannane

The chemistry of *o*-benzoquinones, especially their involvement in cycloadditions, has been the subject of extensive investigations in recent years (Nair and Kumar 1994, 1996a, b). In contrast, their aza analogs, viz., *o*-quinonediimines, have received only scant attention (Friedrichsen and Bottcher 1981), the available information on their cycloadditions being mainly concerned with their participation in Diels–Alder reactions with alkenes (Friedrichsen and Schmidt 1978).

In 2004 Nair and coworkers reported that a facile reaction occurred when a solution of 4-chloro-*o*-quinoneimine dibenzenesulfonimide (Adams and Winnick 1951) **263a** (R^1 = Cl, R^2 = H) was exposed to allyltri-*n*-butyltin **264** in the presence of $ZnCl_2$. The reaction mixture on workup afforded the tetrahydroquinoxaline derivative **265a** (instead of the expected dihydroindole derivative **265a′**) as a colorless crystalline solid in 98 % yield (Scheme 2.38) (Nair et al. 2004b). A similar reactivity was displayed with other substituted *o*-quinonedibenzenesulfonimides **263b–e** (Scheme 2.37) (Nair et al. 2004b).



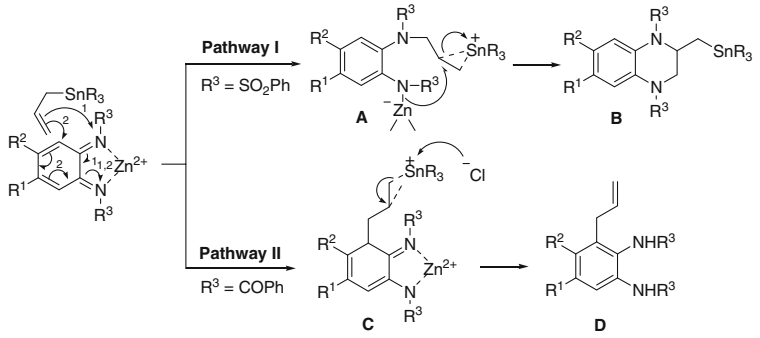
Scheme 2.37 Lewis acid-promoted annulation of *o*-quinonedibenzenesulfonimides **263** using allylstannane **264**



Scheme 2.38 Lewis acid-promoted annulation of *o*-quinoneimine dibenzimides **266** with allylstannane **264**

However, the $ZnCl_2$-catalyzed reaction of *o*-quinoneimine dibenzimide **266a** ($R^1 = R^2 = H$) and allylstannane **264** resulted in the formation of ring-allylated amide **267a**. In the case of other substituted *o*-quinonedibenzimides **266**, allylation took place in a 1,4- or 1,6-manner depending on the ring substituents (Scheme 2.38) (Nair et al. 2004b).

According to the authors' opinion (Nair et al. 2004b), the mechanistic dichotomy underlying the reaction leading to an allylated product in the case of benzimide versus Diels–Alder adducts with sulfonamide may be resolved as follows (Scheme 2.39). Since the Lewis acid is crucial for the formation of tetrahydroquinoxaline derivatives, it is suggested that an ionic mechanism operates in this transformation. First, the Lewis acid coordinates with the quinone imine. The initial attack of allylstannane mainly depends on the basicity of the quinone imine nitrogen. The sulfonyl substituent on nitrogen is more electron-withdrawing, and allylstannane attacks it to form an intermediate tin-coordinated carbocation that is stabilized by a hyperperconjugative interaction with the tin (Herndon and Wu 1989; Herndon et al. 1991). The carbocation **A** thus formed is quenched by the *N*-terminus of the metal-coordinated nitrogen to furnish product **B** (*Pathway I*). When the N-substituent is benzoyl (imide nitrogen is more basic), the initial nucleophilic attack by the allylstannane occurs in a 1,4- or 1,6-manner depending on the substituents on the aromatic ring. The resulting carbocation **C** suffers destannylation to furnish the product **D** (*Pathway II*).



Scheme 2.39 The mechanistic dichotomy of the reaction

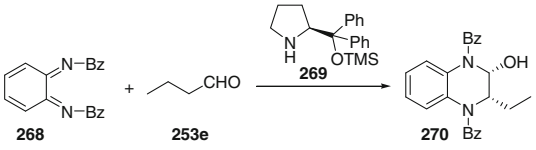
2.3.2 With Aldehydes

In 2006, Lectka and coworkers reported an asymmetric inverse electron demand hetero-Diels–Alder reaction (HDAR) of acyl chlorides (Bekele et al. 2006; Wolfer et al. 2006) and *o*-benzoquinone diimides to deliver chiral quinoxalinones (Abraham et al. 2006). In spite of perfect ee values observed by the catalysis of Lewis bases derived from cinchona alkaloids, the reaction conditions were somewhat harsh and metal triflates had to be used as co-catalysts to activate the electrophilic *o*-benzoquinone diimides (Abraham et al. 2006; Paull et al. 2008).

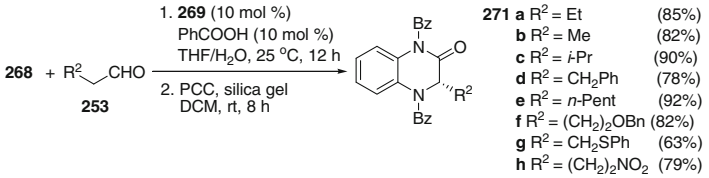
Since the required *o*-benzoquinone diimide was easily accessible by benzoylation of commercially available 1,2-DAB derivative and subsequent oxidation, it appears possible that a search for more appropriate methods of carrying out HDAR to synthesize chiral quinoxaline derivatives would be fruitful.

In 2009, Chen and coworkers reported a highly enantioselective organocatalytic inverse electron demand HDAR reaction of *o*-benzoquinone diimides and aliphatic aldehydes catalyzed by α,α-diphenylprolinol *O*-TMS ether **269** as a chiral secondary amine (Scheme 2.40) (Li et al. 2009b).

When the HADR was carried out as in the previously established conditions (Han et al. 2008): *o*-benzoquinone diimide **268** (1.0 equiv), butanal **253e** (2.0 equiv), benzoic acid (10 mol%), and the catalyst α,α-diphenylprolinol *O*-TMS ether **269** (10 mol%) in a mixture of MeCN and H_2O (10:1) at room temperature, the reaction proceeded smoothly and the desired hemiaminal **270** was isolated as a



Scheme 2.40 Optimization of the organocatalytic HDAR of the *o*-benzoquinone diimides **268** and butanal **253e**



Scheme 2.41 Asymmetric inverse electron demand HDAR of *o*-benzoquinone diimides **268** and aldehydes **253**

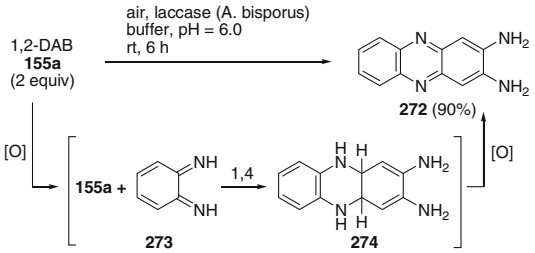
relatively stable compound with excellent stereoselectivity (ee 97 %) and good yield (71 %). Even more satisfactory yields could be attained in a mixture of 1,4-dioxane/H_2O (ee > 99 %, yield 83 %) or THF/H_2O (ee > 99 %, yield 89 %) (10:1).

The scope of this asymmetric HDAR was evaluated under the optimized reaction conditions using *o*-benzoquinone diimide **268**. Since the hemiaminal **270** was not stable enough for further analysis, PCC (pyridinium chlorochromate) oxidation was employed to produce the more stable quinoxalinones **271**. As shown in Scheme 2.41, a variety of aldehydes **253** bearing simple linear or branched α-substituted alkyl groups were well tolerated and excellent enantioselectivities were generally obtained.

2.3.3 With 1,2-DAB

In the context of the discussion above, it should be noted that the oxidative transformation of 1,2-DAB **155a** with air as an oxidant in the presence of catalytic amounts of laccase from *Agaricus bisporus* delivers exclusively 2,3-diaminophenazine **272** in 90 % yield (Scheme 2.42) (Leutbecher et al. 2011). It is assumed that the oxidative dimerization of **155a** starts with the laccase-catalyzed oxidation of one molecule of the substrate to the corresponding diimine **273**, which reacts with a second molecule of **155a** by means of an inter- and an intramolecular 1,4-addition to yield a tetrahydrophenazine **274**. The last step is the oxidation of this intermediate to afford the fully aromatic 2,3-diaminophenazine **272**. On an

Scheme 2.42 Preparation of 2,3-diaminophenazine **272** by laccase-catalyzed aerobic dimerization of **155a**



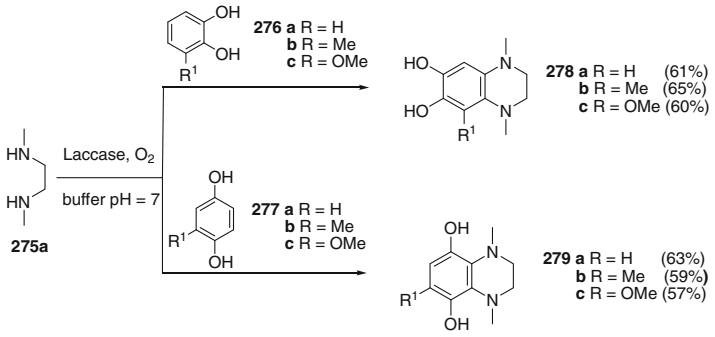
analytical scale this reaction has been employed for determining the activity of laccases (Zuyun et al. 1998). Alternatively, this transformation can also be performed on a preparative scale with either $FeCl_3$ (Chauhan et al. 2008) or hydrogen peroxide in the presence of catalytic amounts of peroxidases (Niu et al. 2004).

2.4 Condensation of *N*,*N*-Dimethyl(dibenzyl) ethylenediamine with 1,2- and 1,4-Dihydroxy Benzenes

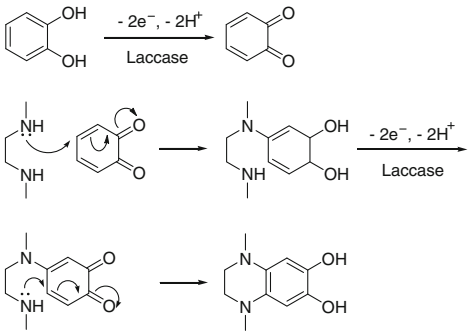
A new series of quinoxaline derivatives have been efficiently synthesized with an environment-friendly catalyst, i.e., enzyme, mainly the laccase isolated from Ganoderma sp. rckk-02. This methodology provides an alternative route safest for the synthesis of quinoxalines. 1,2- and 1,4-Dihydroxy benzenes were used for the first time in the synthesis of quinoxalines (Kidwai et al. 2012) (Scheme 2.43).

For the mechanistic aspects of this new transformation, the first oxidation of the dihydroxy benzene to the corresponding ketone was assumed to occur followed by an electron-deficient site reaction with diamine. Although intermediate is a 1,2-diketone but in this case, it does not react in a same manner as for quinoxaline synthesis via the classical method (Xu et al. 2007; Kunamneni et al. 2008; Witayakran and Ragauskas 2009; Ma et al. 2009; He et al. 2010; Guncheva and Zhiryakova 2011). In this case its electron-deficient site is more prone to be attacked by amine (Scheme 2.44).

The ambient condition, use of natural source in place of oxidative reagents, not only makes this methodology an alternative platform to the conventional route for the same, but it also becomes significant under the umbrella of environmental greener and safer processes.



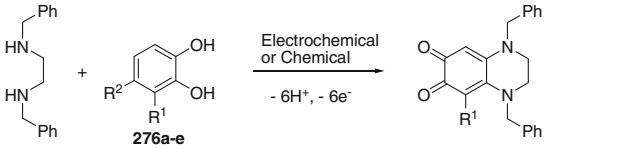
Scheme 2.43 Reaction between *N*,*N*-dimethylethylenediamine **275a** and different 1,2- and 1,4-dihydroxy benzene **276**, **277** in the presence of laccase at room temperature



Scheme 2.44 Plausible mechanism for the synthesis of quinoxaline derivatives in the presence of laccase at room temperature

Chemical and electrochemical oxidations of different catechols were carried out in the presence of *N*,*N*′-dibenzylethylenediamine (DBEDA) in a phosphate buffer/acetonitrile solution for the synthesis of different new dibenzyltetrahydroquinoxalinedione derivatives (Habibi et al. 2014). The oxidation of catechol **276a**, 2,3-dihydroxybenzoic acid **276e**, and 3,4-dihydroxybenzoic acid **276d** led to the same product, probably due to the decarboxylation reaction of intermediates. An oxidative decarboxylation reaction of 3,4-dihydroxybenzoic acid **276d** was reported earlier, while the unexpected oxidative decarboxylation reaction of 2,3-dihydroxybenzoic acid **276e** in the presence of DBEDA has been reported for the first time (Scheme 2.45).

The formation of **280a–c** was followed by the 1,4-Michael addition of DBEDA to the quinone to produce the adducts **281a–c**. These adducts then underwent the abstraction of a second pair of electrons leading to *o*-benzoquinone **282a–c**. Intramolecular addition produces catechol derivatives **283a–c** and the further oxidation of these compounds led to the formation of the final products **284a–c**. The oxidation of intermediates **281a–c** and **283a–c** is simpler than the oxidation of the parent starting molecules **276a–c** due to the presence of the electron-rich amino groups on the quinone ring. Besides, it is possible that the oxidation of **281a–c** and **283a–c** takes place through a solution electron transfer reaction (Scheme 2.46) (Habibi et al. 2006).



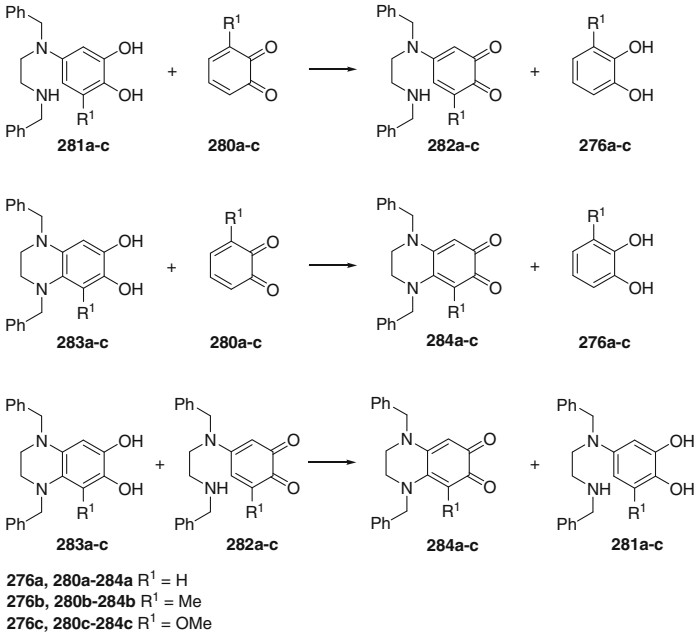
275b

276a-e

276 d R^1 = H, R^2 = CO_2H
e R^1 = CO_2H, R^2 = H

284 a R^1 = H (98%, 36%)
b R^1 = Me (98%, 42%)
c R^1 = OMe (66%, 28%)

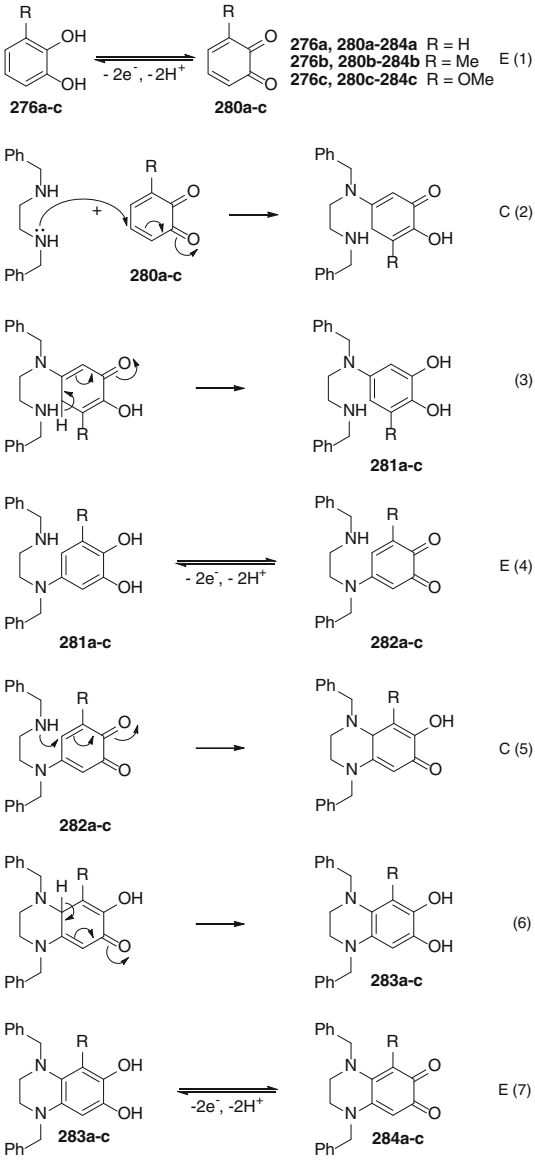
Scheme 2.45 Synthesis of different dibenzyltetrahydroquinoxalinedione derivatives



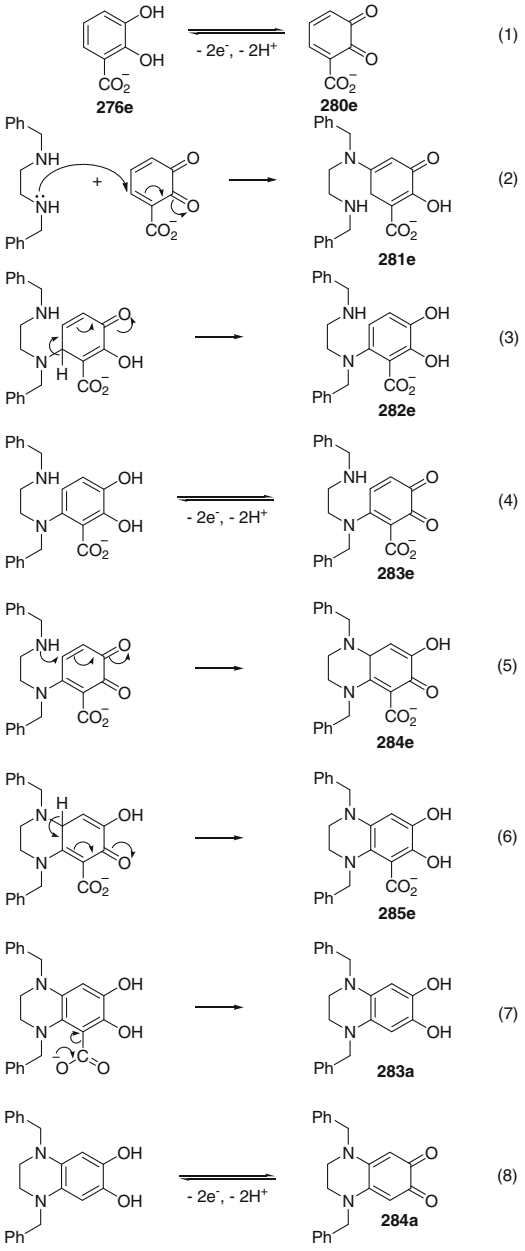
Scheme 2.46 Solution electron transfer reaction

Different catechols **276a–e** were oxidized by chemical or electrochemical methods in the mixture of phosphate buffer solution (PBS) and MeCN solution to their *o*-benzoquinones and then attacked by DBEDA to form the corresponding dibenzyltetrahydroquinoxalinedione derivatives **284a–c**. The overall reaction mechanisms for the anodic oxidation of these derivatives in the presence of DBEDA as a nucleophile are presented in Schemes 2.46 and 2.47. An unexpected oxidative decarboxylation reaction of 2,3-dihydroxybenzoic acid **276e** in the presence of DBEDA is shown in Scheme 2.48. Three pathways for the synthesis of 1,2,3,4-tetrahydroquinoxaline-6,7-dione **284a** have been introduced. From the point of view, of green chemistry the application of the electro-synthetic method has some important advantages. Clean synthesis, use of electricity as an alternative source of energy instead of oxidative reagents, a one-step reaction, working at room temperature, technical feasibility, and high atom economy are prominent advantages of the green approach. Both chemical and electrochemical methods result in the same products. While the chemical synthesis is faster, the electrochemical synthesis provides higher yields.

Scheme 2.47 Proposed mechanism for the electrochemical oxidation of **276a–c** in the presence of DBEDA



Scheme 2.48 Proposed mechanism for the oxidation of **276e** in the presence of DBEDA

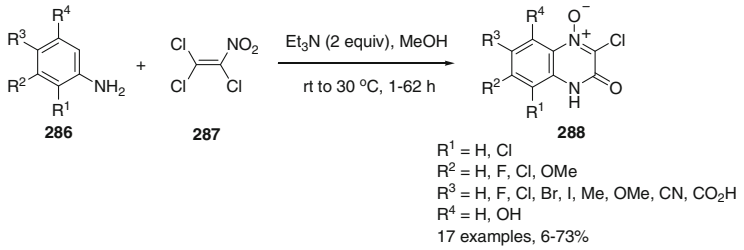


2.5 Synthesis of Quinoxalines from Aniline and Its Derivatives

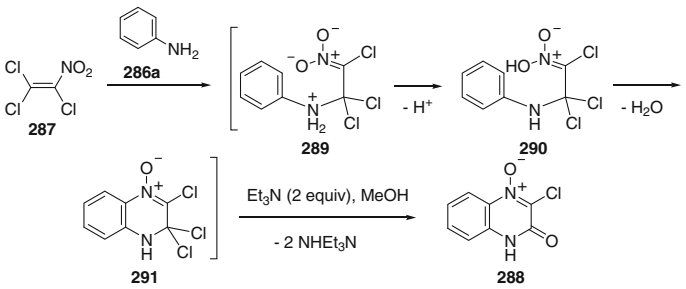
2.5.1 From Anilines

A one-pot annulation reaction of aniline and its ring-substituted derivatives with 1,1,2-trichloro-2-nitroethene (TCNiE) was developed delivering exclusively 3-chloroquinoxalin-2(1*H*)-one 4-oxides in good yields (Meyer et al. 2008). If one equivalent of aniline or a derivative **286** and two equivalents of a tertiary amine such as triethylamine (TEA) or 1,4-diazabicyclo[2.2.2]octane (DABCO) were added to a solution of **287** in a solvent such as methanol, tetrahydrofuran, or toluene, the new quinoxalin-2(1*H*)-one 4-oxide **288** precipitated completely (Scheme 2.49) (Meyer et al. 2008). The yield of the product depended on the reaction temperature, the addition rate of the aniline to the reaction mixture, the solvent, and the substitution pattern of the aniline.

The mechanism of this new one-pot annulation reaction between TCNiE and anilines has been extensively investigated with the help of the B3LYP/6-31 + G** methodology and five different paths were proposed (Meyer et al. 2008). The main stages of these mechanisms include the following processes: the sequence starts with the Michael addition of the aromatic amine at the C(2) position of TCNiE **287** forming an intermediate such as **289**. *N*-Alkylanilines do not form quinoxalinones. Later, a proton shift occurs: the ammonium proton migrates to the nitro group thus forming nitronic acid **290**. In the following stages, an intramolecular S_E process appears feasible leading to cyclisation via C–N bond formation, elimination of water, and then generation of 2,2,3-trichloro-1,2-dihydroquinoxaline 4-oxide **291**. Hydrolysis of the *gem*-C(2) dichloride unit in **291** by water in the reaction mixture leads to the formation of the final product **288**, even in dry solvents (Scheme 2.50).



Scheme 2.49 Formation of quinoxalinone 4-oxides **288** starting from anilines **286**

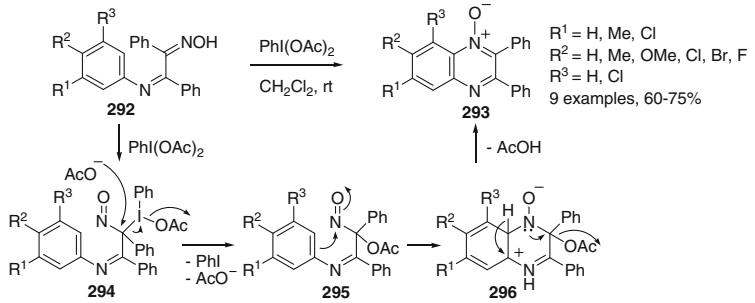


Scheme 2.50 Postulated mechanism for the formation of **288**

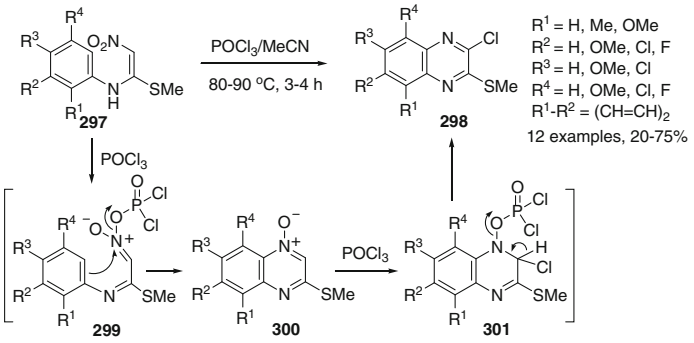
2.5.2 *From Benzil-α-arylimino Oximes and α-Nitroketene* N,S-*Anilinoacetals*

Benzil-α-arylimino oximes **292** (Aggarwal et al. 2006) and α-nitroketene *N*,*S*-anilinoacetals **297** (Venkatesh et al. 2005), containing a C–C–N fragment at the aniline nitrogen atom when exposed to, respectively, iodobenzene diacetate PhI $(OAc)_2$ (IBD) and $POCl_3$, undergo cyclization with the formation of the 2,3-diphenylquinoxaline-1-oxide **293** (Scheme 2.51) and 3-chloro-2-(methylthio) quinoxaline **298** (Scheme 2.52) derivatives, respectively.

As can be seen from in Scheme 2.51, a plausible mechanism for the transformation of **292** into **293** involves the initial electrophilic attack of IBD on the oxime **292** and results in an I(III) intermediate **294**, which undergoes the reductive loss of iodobenzene along with the elimination of acetic acid to afford nitroso derivative **295**. Cyclization of **295** via an entropy favored electrophilic process gives an intermediate **296**, which loses a second mole of acetic acid to yield quinoxaline *N*-oxide **293** (Aggarwal et al. 2006).



Scheme 2.51 Hypervalent iodine oxidation of benzil-α-arylimino oximes **292** is an efficient synthesis of 2,3-diphenylquinoxaline 1-oxides **293**

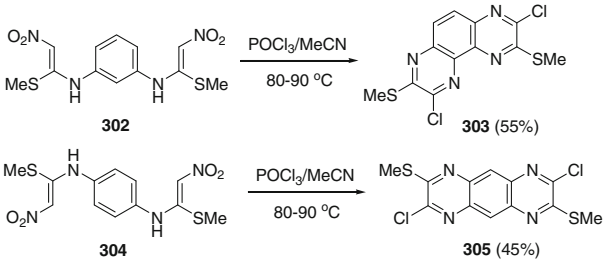


Scheme 2.52 Heteroannulation of nitroketene *N*,*S*-arylaminoacetals **297** with $POCl_3$

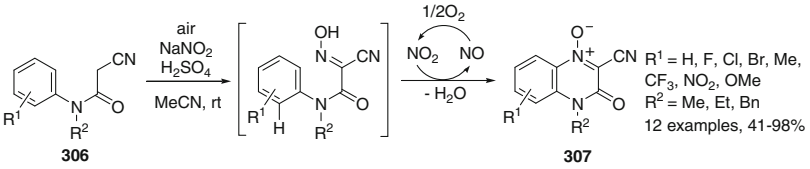
The probable mechanism for the conversion of *N*,*S*-acetals **297** into quinoxalines **298** involves the initial formation of quinoxaline *N*-oxide **300** by dehydrative cyclization of **297** followed by a subsequent chlorination at the 3-position and the extrusion of oxygen through intermediate **301** (Scheme 2.52) (Venkatesh et al. 2005).

To further explore the generality and scope of this new quinoxaline synthesis, the reaction was extended to bis-(nitroketene *N*,*S*-acetals) **302** and **304** which under identical conditions afforded the hitherto unknown pyrazinoquinoxalines **303** and **305** in 55 and 45 % yields, respectively (Scheme 2.53) (Venkatesh et al. 2005).

In 2011, Kobayashi and coworkers reported a highly efficient method for constructing quinoxalin-2(1*H*)-one 4-oxide through the tandem nitrosation/aerobic oxidative cyclization of cyanoacetanilides with inexpensive reagents. A mechanistically novel oxidative aromatic C–N bond-forming reaction of *aci*-nitroso species **306** was suggested utilizing molecular oxygen as the sole oxidant (Scheme 2.54) (Kobayashi et al. 2011). The CN groups of **307** were successfully substituted not only with a carbon nucleophile but also a nitrogen nucleophile. This strategy enables rapid access to various substituted quinoxalinone *N*-oxides.



Scheme 2.53 Heteroannulation of 1,3- and 1,4-bisnitroketene *N*,*S*-arylaminoacetals **302** and **304** with $POCl_3$



Scheme 2.54 Tandem nitrosation/aerobic oxidative cyclization of cyanoacetanilides **306**

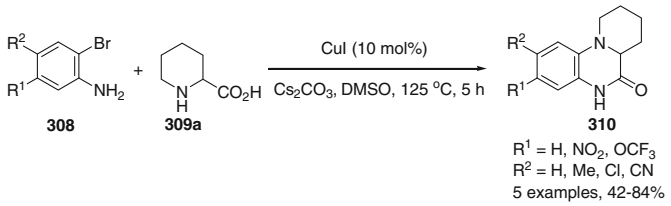
2.5.3 From 2-Haloanilines

In 2009, Tanimori and coworkers reported a new efficient method for synthesizing quinoxalin-2-ones in up to an 86 % yield, based on reactions of 2-haloanilines with a variety of α-amino acids, such as pipecolinic acid and its bicyclic analog—1,2,3,4-tetrahydroisoquinoline 3-carboxylic acid and D,L-proline in the presence of copper(I) iodide. A variety of 2-bromoanilines **308** with substituents on the aromatic ring which include both electron-donating and electron-withdrawing groups reacted to provide the corresponding dihydroquinoxalin-2-ones **310** (Scheme 2.55) (Tanimori et al. 2009).

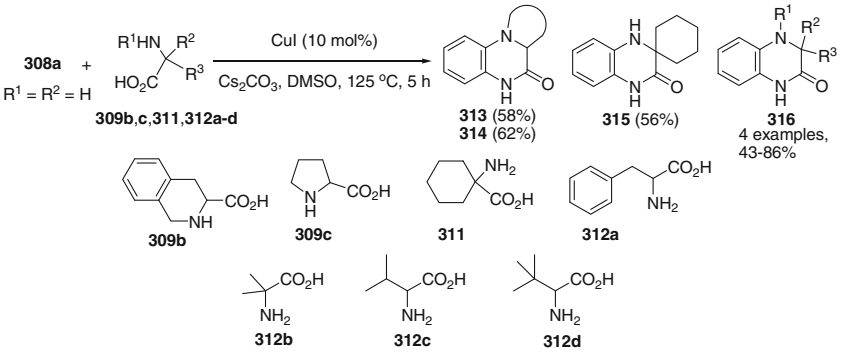
The use of various α-amino acids such as **309b**, **c**, **311**, **312a–d** instead of pipecolinic acid **309a** in the reaction with 2-bromoaniline **308a** in the presence of copper(I) iodide made it possible to synthesize various annulated (in the cases of **309b**, **c**), spiro (in the cases of **311**), and 3-substituted (in the cases of **312a–d**) quinoxalines **313**, **314**, **315,** and **316** (Scheme 2.56) (Tanimori et al. 2009).

In the cases of 2-iodo- and 2-chloroanilines the yields of desired 3-substituted dihydroquinoxalin-2-ones were, at best, 63 and 65 %, respectively, and unlike 2-bromoanilines did not depend on the reaction conditions (Tanimori et al. 2009).

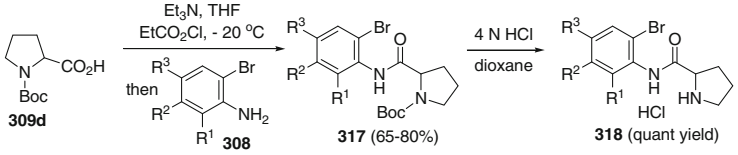
In 2010, Luo and coworkers reported a practical and highly efficient route to the synthesis of pharmaceutically interesting quinoxalinones (Luo et al. 2010). The key step involves an intramolecular palladium-catalyzed *N*-arylation reaction (Buchwald–Hartwig amination Janey 2007; Appukkuttan and Van der Eycken 2008) under microwave irradiation. The precursors to the quinoxalinone core were easily prepared from D,L-proline **309d** in accordance with the mixed anhydride protocol followed by Boc group deprotection (Scheme 2.57).



Scheme 2.55 Reactions of substituted 2-bromoanilines **308** with pipecolinic acid **309a**



Scheme 2.56 Reactions of 2-bromoaniline **308a** with various α-amino acids **309b**, **c**, **311**, **312a–d**

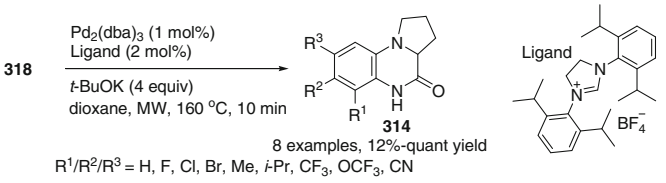


Scheme 2.57 Synthesis of substituted bromoanilides **318**

The resulting amine hydrochloride salts were obtained with sufficient purity (>95 %) and were directly used for cyclization. The general reaction conditions required 1 mol% of $Pd_2(dba)_3$, 2 mol% of 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium tetrafluoroborate as a ligand and four equivalents of *t*-BuOK. The mixture was heated in 1,4-dioxane at 160 °C for 10 min in a microwave reactor (Scheme 2.58). The crude product was typically purified by simply passing the crude reaction mixture through a short pad of silica gel.

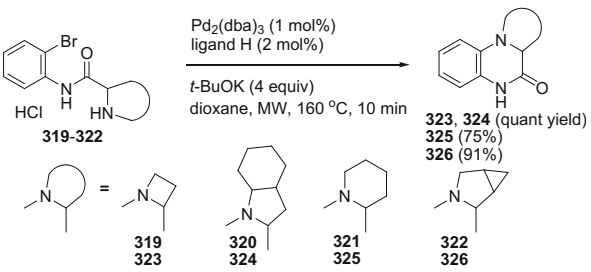
This methodology tolerates a variety of bromoanilides **319–322** to afford a diverse collection of bicyclic and polycyclic quinoxalinones **323–326** in high yields (Scheme 2.59).

At mild room temperature, ligand-free copper-catalyzed coupling of α-amino acids **312a**, **c**, **e**, **328**, including heretofore-unexplored arylglycines **312a**, with *N*-Boc-2-iodoanilines **327** to deliver *N*-arylated α-amino acids **329** has been developed



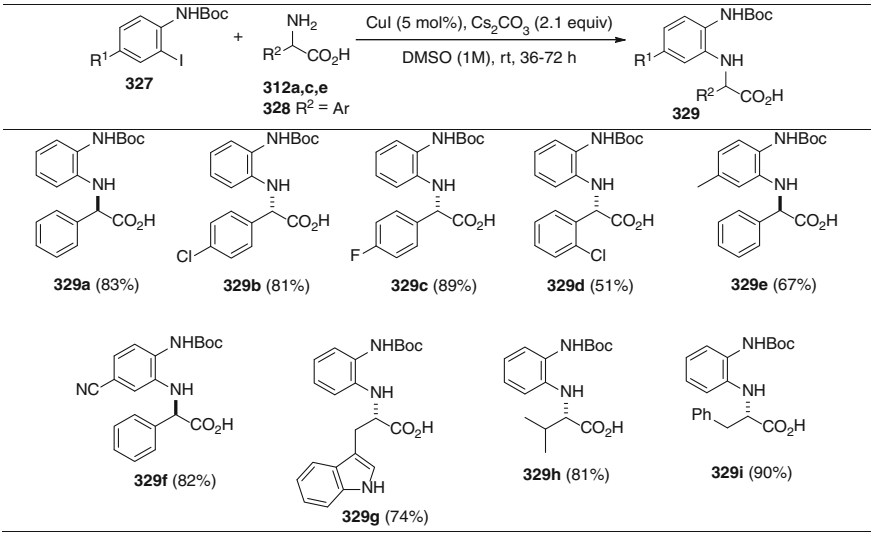
Scheme 2.58 Palladium-catalyzed cyclization of substituted bromoanilides **318**

Scheme 2.59 Synthesis of polycyclic quinoxalinones **323–326**

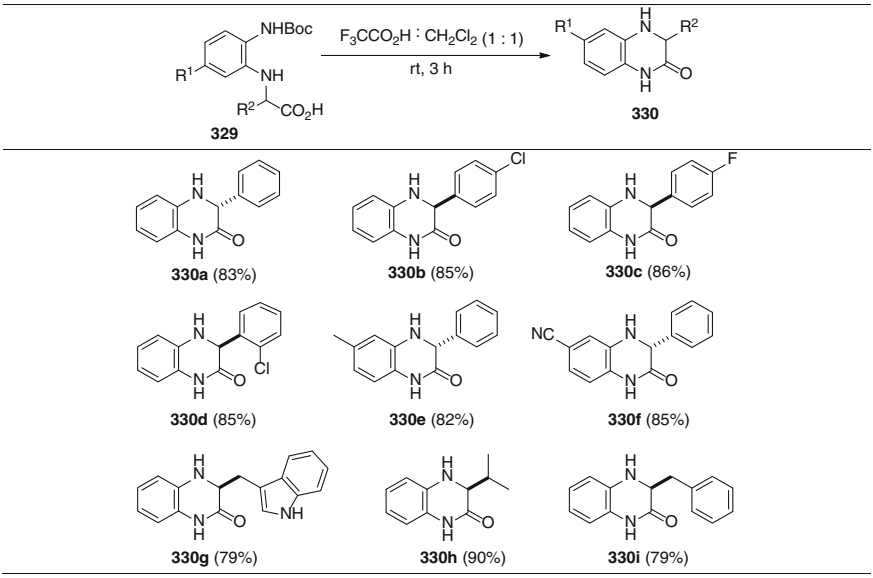


(Scheme 2.60) (Luo and De Brabander 2015). These adducts **329** were transformed into chiral 3-substituted 3,4-dihydroquinoxalin-2(1*H*)-ones **330** (Scheme 2.61) upon trifluoroacetic acid-mediated Boc deprotection/in situ cyclodehydration. Importantly, the entire two-step procedure occurs without racemization, even with racemization-prone arylglycine substrates. This approach uniquely avoids potential symmetry-related limitations in the substrate scope compared to previous approaches to enantiomerically pure 3-aryl-3,4-dihydroquinoxalin-2(1*H*)-ones that emanate from symmetrical dianilines.

In 2006, Kalinski and coworkers reported a new strategy employing an Ugi four-component reaction (4CR) and a Pd-assisted intramolecular *N*-aryl amidation reaction (Kalinski et al. 2006). The Ugi(4CR) reaction of 2-bromoanilines **308**, ketones/aldehydes **198e**, **253l**, carboxylic acid **331,** and an isocyanide **254a**, **h**, **i** in polar protic solvents (methanol, trifluoroethanol) generally resulted from good to



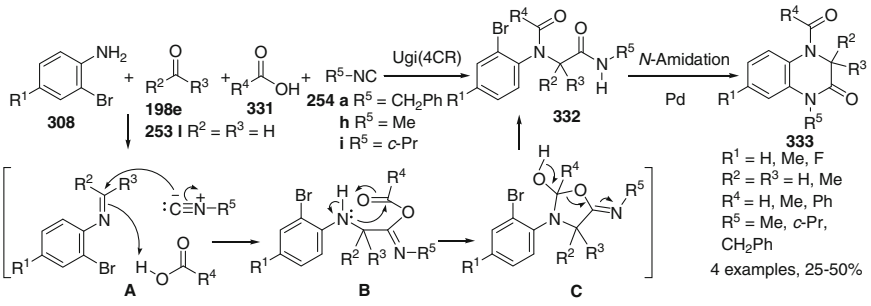
Scheme 2.60 Cross-coupling of *N*-Boc-2-iodoanilines **327** with α-amino acids **328**, **312a**, **c**, **e**. For **329a–f**, the ee was determined to be ≥98 % as determined by chiral stationary phase HPLC analysis using racemic products



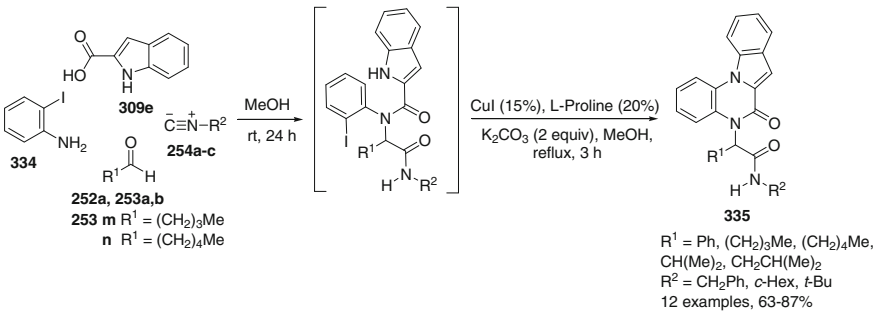
Scheme 2.61 Acid-mediated cyclization of **329** to 3-substituted-dihydroquinoxalinones **330**. For compounds **330a–c**, the ee was determined to be ≥98 % as determined by chiral stationary phase HPLC analysis using racemic products

high yields, and thus amides **332** were formed through the intermediates **A**, **B,** and **C**. In the second stage, the Ugi product **332** was dissolved in toluene and the *C*-amidation was performed at 100 °C using the catalytic system tris(dibenzylideneacetone) di-palladium $Pd_2(dba)_3$, tri-*o*-tolylphosphine as a ligand and a carbonate base (Cs_2CO_3 with aliphatic isocyanides or K_2CO_3 with benzylic isocyanides). The expected dihydroquinoxalin-2-ones **333** were obtained with moderate to good yields (Scheme 2.62) (Kalinski et al. 2006).

Similarly, the Ugi four-component reaction of aldehydes **252a**, **253a**, **b**, **m**, **n**, 2-iodoaniline **334**, indole-2-carboxylic acid **309e**, isocyanides **254a–c,** and



Scheme 2.62 A plausible mechanism for the formation of dihydroquinoxalin-2-ones **333**



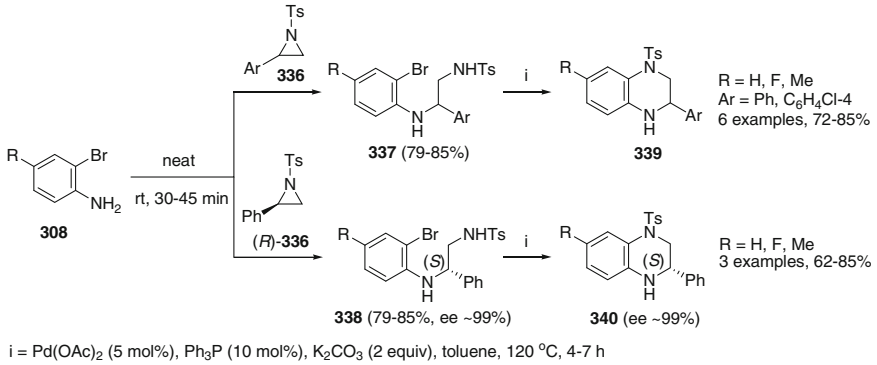
Scheme 2.63 Synthesis of indolo[1,2-*a*]quinoxalines **335** via sequential Ugi/Ullmann reaction

subsequent intramolecular *N*-arylation of the Ugi adduct provides a new, mild strategy to assemble tetracyclic indolo[1,2-*a*]quinoxalinones **335** in the presence of catalytic amounts of CuI and L-proline in methanol at reflux (Ullmann process) (Scheme 2.63) (Balalaie et al. 2011).

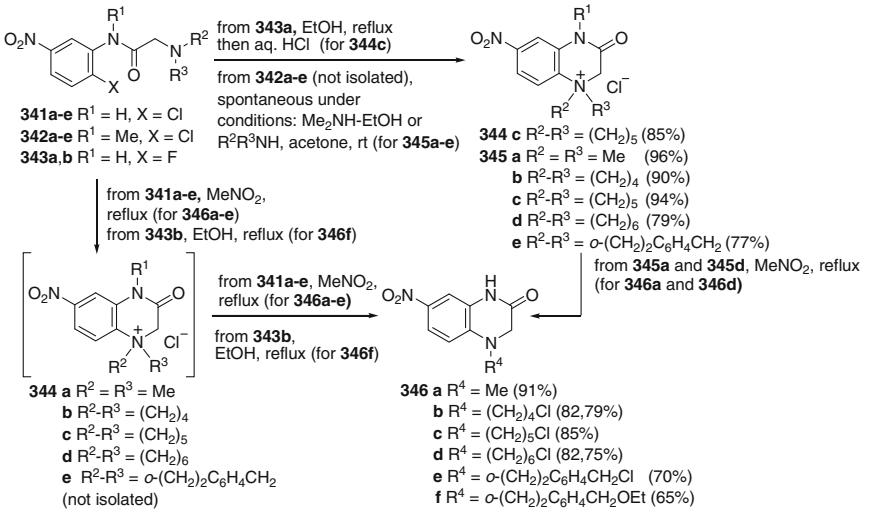
A highly regio- and stereoselective route for the synthesis of racemic **339** and nonracemic **340** substituted tetrahydroquinoxalines used the S_N2-type ring opening of activated aziridines with 2-bromoanilines followed by the Pd-catalyzed intramolecular C–N bond formation (Scheme 2.64) (Ghorai et al. 2011).

When bicyclic *N*-tosylcyclohexene and cyclopentene aziridines were used with various 2-bromoanilines the process easily provided cyclohexa- and cyclopenta-annulated tetrahydroquinoxalines with up to 80 % yields (Ghorai et al. 2011).

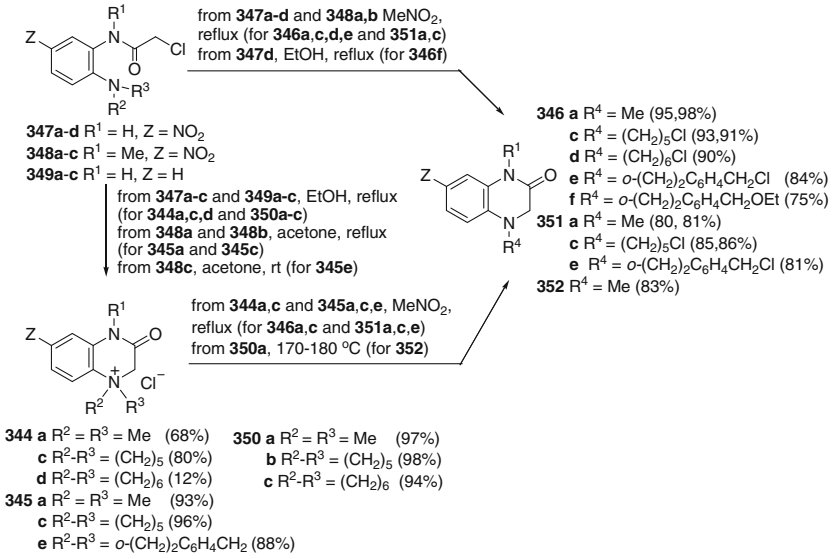
Two different, simple, and efficient methods for synthesizing quinoxaline derivatives start, respectively, from 2-dialkylamino-2′-halogeno-5′-nitroacetanilides **341**–**343** (Scheme 2.65) or from 2′-dialkylamino-2-halogenoacetanilides **347**–**349** (Scheme 2.64) (De Castro et al. 2002). Both types of acetanilide are initially cyclized to 1,1-disubstituted 3-oxoquinoxalinium salts **344a**–**e**, **345a**–**e** (Scheme 2.65) and **344a**, **c**, **d**, **345a**, **c**, **e**, **350a**–**c** (Scheme 2.66) through intramolecular quaternization



Scheme 2.64 Synthetic routes to racemic and nonracemic 1,2,3,4-tetrahydroquinoxalines via the ring opening of *N*-tosyl aziridines

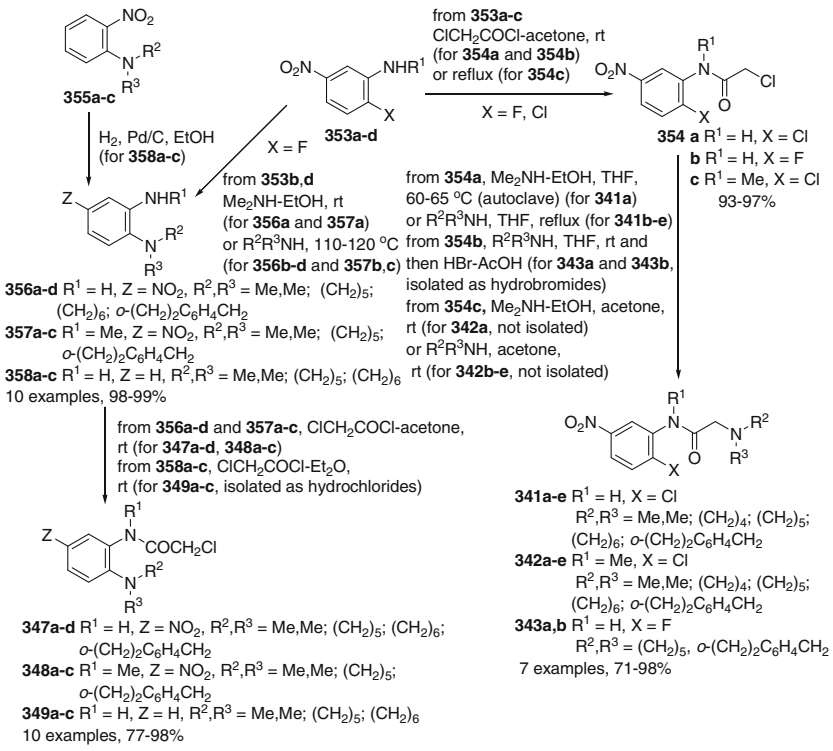


Scheme 2.65 The synthesis of quinoxaline derivatives starting from 2-dialkylamino-2′-halogeno-5′-nitroacetanilides **341**–**343**



Scheme 2.66 The synthesis of quinoxaline derivatives starting from 2′-dialkylamino-2-halogenoacetanilides **347**–**349**

reactions. These salts are converted by heating, sometimes without isolation, under the conditions required for the cyclization of the corresponding acetanilides **341**–**343**, **347**–**349** into 4-substituted quinoxalin-2-ones **346**, **351**, **352**.



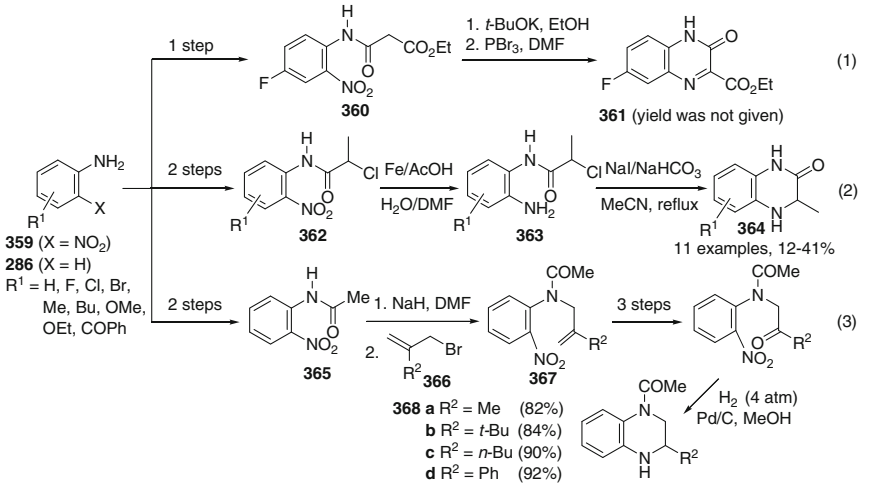
Scheme 2.67 Synthesis of 2-dialkylamino-2′-halogenoacetanilides **341**–**343** and 2′-dialkylamino-2-halogenoacetanilides **347**–**349** as precursors to quinoxalinones

Compounds **341**–**343** and **347**–**349** were subsequently synthesized starting from 2-halo-*N*-alkyl-5-nitroanilines **353a**–**d** according to the pathways shown in Scheme 2.67.

2.5.4 From Nitroanilines

The strategy for the synthesis of quinoxalines from nitroanilines also involves two stages, but in this case, the first stage consists of the introduction of a two-carbon fragment containing functional groups capable of reacting with the amino group with closure of the pyrazine ring. The second stage of the reaction involves tandem reduction and reductive amination.

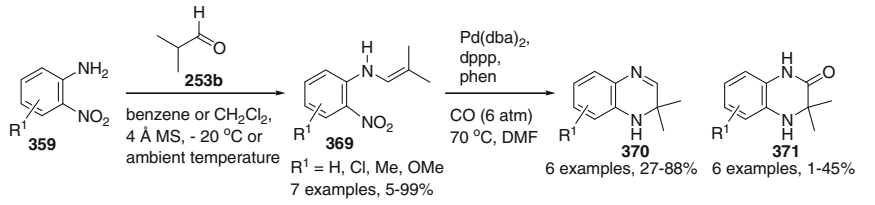
Ethyl malonyl chloride (Scheme 2.68, Eq. 1) (Takano et al. 2003), α-chloropropionyl chloride (Scheme 2.68, Eq. 2) (Li et al. 2005), allylic halides (Scheme 2.68, Eq. 3) (Bunce et al. 2003), and aliphatic aldehydes (Wallace et al. 2008) are used the



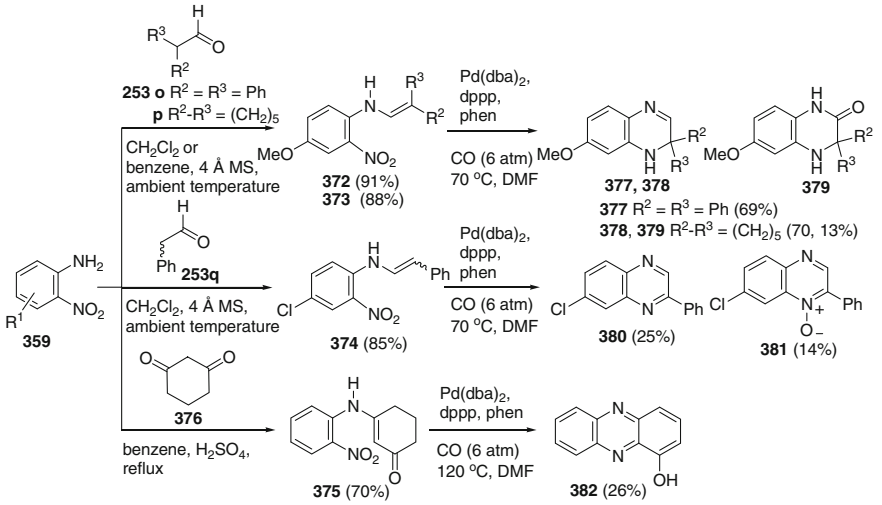
Scheme 2.68 Common strategies for the synthesis of quinoxalines starting from nitroanilines

two-carbon fragment. PBr_3, DMF (Takano et al. 2003), Fe/AcOH (Li et al. 2005), H_2/Pd/C, MeOH (Bunce et al. 2003) (Scheme 2.68) and bis(dibenzylideneacetone)-palladium(0) ($Pd(dba)_2$), 1,3-bis(diphenylphosphino)propane (dppp), and 1,10-phenanthroline (phen) in DMF (Scheme 2.69) (Wallace et al. 2008) are used as reducing agents.

In addition to the enamine **369** described in Scheme 2.69, the other four enamines **372**–**375** obtained from nitroanilines **359** and diphenylacetaldehyde **253o**, cyclohexanecarboxaldehyde **253p**, *trans*-cinnamaldehyde **253q,** and 1,3-cyclohexanedione **376** were examined (Scheme 2.70) (Wallace et al. 2008). The condensation of aldehydes **253o–q** and 1,3-cyclohexanedione **376** with nitroanilines **359** resulted in enamines **372–375** in 91, 88, 85, and 70 % isolated yields, respectively. The *N*-heteroannulation of **372–375** similarly gave the quinoxaline derivatives **377**, **378**, **379**, **380**, **382** in 69, 70, 13, 25, and 26 % isolated yields. In addition to fully aromatic quinoxaline **195**, the corresponding *N*-oxide **381** was obtained, albeit in lower yields in the case of mono-phenyl substituted enamine **374**.



Scheme 2.69 Palladium-catalyzed synthesis of quinoxaline derivatives **370**, **371** starting from nitroanilines and 2-methylpropanal **253b**

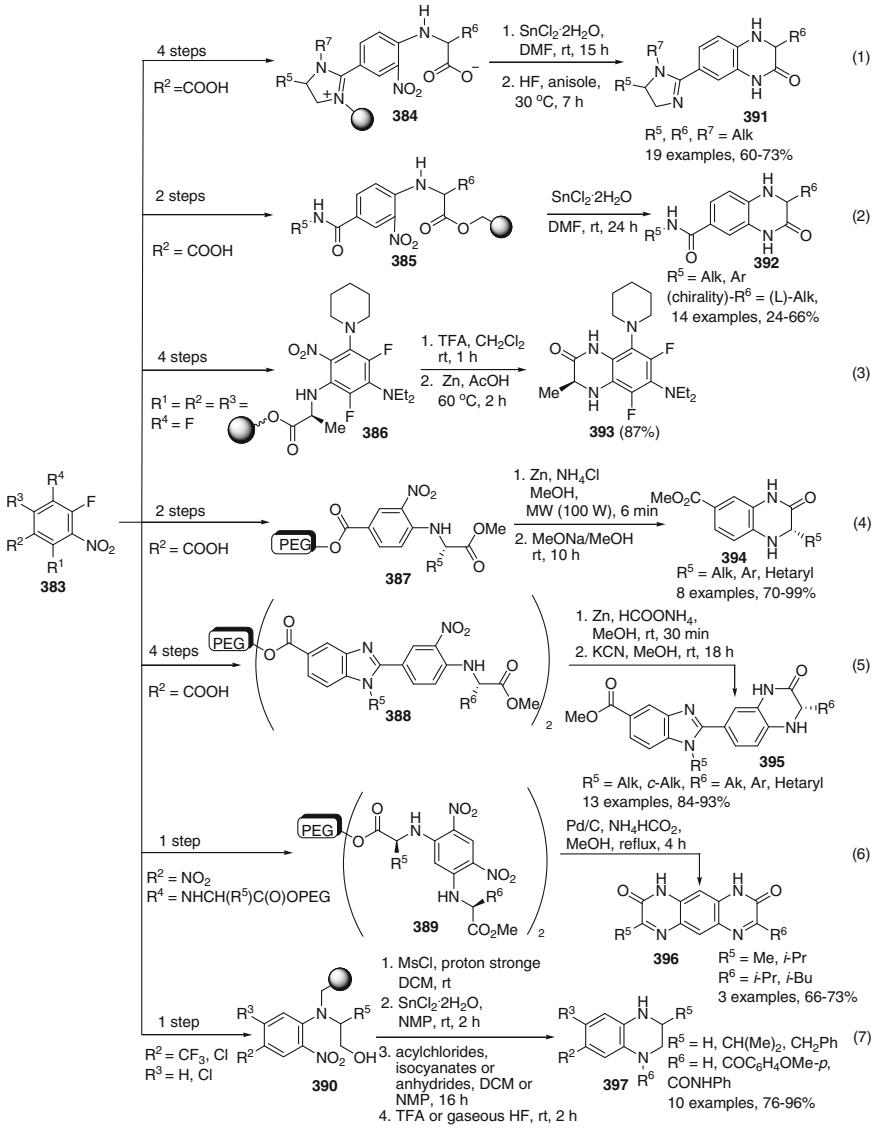


Scheme 2.70 Palladium-catalyzed synthesis of quinoxaline derivatives starting from nitroanilines and a variety of aldehydes **253o**, **p**, **q** or 1,3-cyclohexanedione **376**

2.5.5 From 2-Fluoro-1-nitrobenzenes

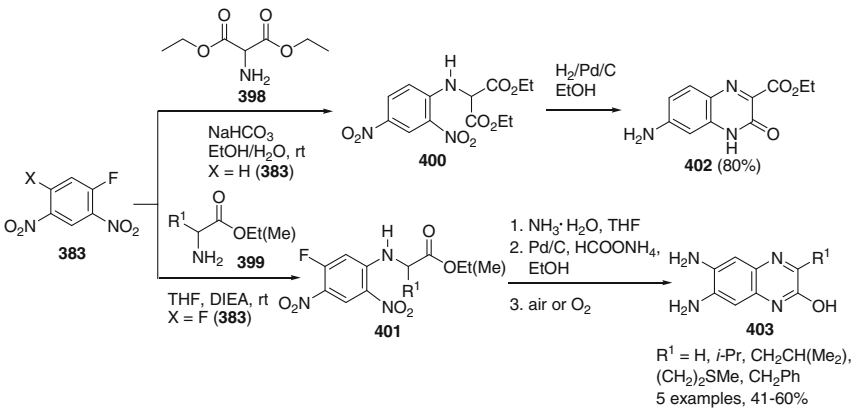
The methods of the synthesis of quinoxalines from 2-fluoro-1-nitrobenzenes involve two basic steps: (a) a nucleophilic aromatic substitution and (b) a reductive cyclization with the formation of a nitroaniline derivative. In this case, the reagent, allowing a three-atom N–C–C fragment to be introduced as a result of nucleophili-caromatic substitution, should contain a form of functional group capable of reacting with the amino group and closing the pyrazine ring under the conditions for reduction of the nitro group. A variety of aminoacetic acid derivatives, coupled to the *p*-methylbenzhydrylamine resin (Scheme 2.71, Eq. 1) (Acharya et al. 2002), preloaded onto the Wang resin (Scheme 2.71, Eq. 2) (Laborde et al. 2001), coupled to L-alanine HMB and other natural amino acid ester resins (1 % DVB polystyrene) (Scheme 2.71, Eq. 3) (Holland et al. 2002), and the soluble polymer support (PEG) (Scheme 2.71, Eq. 4) (Tung and Sun 2004), (Scheme 2.71, Eq. 5) (Chanda et al. 2009), (Scheme 2.71, Eq. 6) (Shen et al. 2012; Lai et al. 2010) and derivatives of secondary amino alcohols, fixed on the polymer of 4-(4-formyl-3-methoxyphenoxy) butyryl AM resin (Scheme 2.71, Eq. 7) (Krchňák et al. 2001) are used as reagents for the introduction of the three-atom N–C–C fragment.

In other examples utilizing 2-fluoro-1-nitrobenzenes, but not employing a solid support, the catalytic reduction of the diethyl *N*-[(2,4-dinitrophenyl)amino]malonate **400** (Harnik and Margoliash 1955) and ethyl(methyl) *N*-[(2,4-dinitro-5-fluorophenyl) amino]acetate **401** yielded ethyl 6-amino-3,4-dihydro-3-oxoquinoxaline-2-carboxylate **402** and 2-hydroxy-3-*R*-6,7-diaminoquinoxaline **403** (Scheme 2.72). These starting compounds, **400** and **401**, were easily obtained from the **383** and α-amino acid

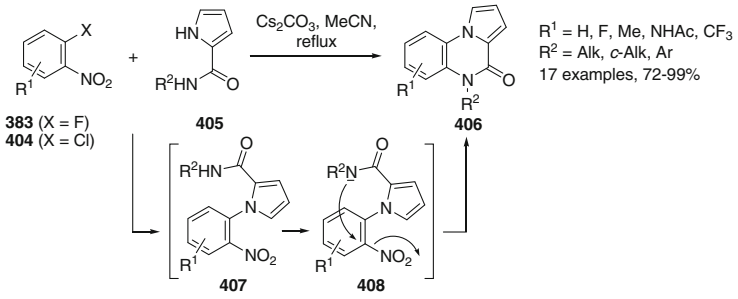


Scheme 2.71 Common strategies for the synthesis of quinoxalines starting from 2-fluoro-1-nitrobenzenes

derivatives **398** (Varano et al. 2001), **399** (Scheme 2.72) (Wu and Gorden 2007; Wu et al. 2007). The quinoxaline derivatives were used for the synthesis of a set of glycine/NMDA receptor antagonists (Varano et al. 2001) and 2-quinoxalinol salen Schiff base ligands (Wu and Gorden 2007).



Scheme 2.72 The synthesis of ethyl 7-aminoquinoxalin-1(2*H*)-one-3-carboxylate **402** and 6,7-diamino-2-quinoxalinols **403**



Scheme 2.73 One-pot synthesis of the pyrrolo[1,2-*a*]quinoxalines **406** and a plausible mechanism for their formation

A variety of pyrrolo[1,2-*a*]quinoxaline derivatives **406** were synthesized in good to excellent yields when pyrrole-2-carboxamides **405** were used instead of α-amino acid derivatives in reactions with 1-fluoro- (**383**) and chloro- (**404**) -2-nitrobenzenes under a mild transition metal-free process (Scheme 2.73) (Huang et al. 2011).

A plausible mechanism of the reaction involves the formation of compound **406** by the nucleophilic substitution by **405** on 2-halonitroarenes **383**, **404** or 1,2-dihalobenzenes (see Sect. 2.7.3) and the formation of carboxamide anion **408**. Finally, an intramolecular nucleophilic reaction of **408** with the displacement of the leaving group by carboxamide anion would lead to pyrrolo[1,2-*a*]quinoxaline **406** (Scheme 2.73).

When indole-2-carboxamides were used instead pyrrole-2-carboxamides it was possible, by analogy, to synthesize indolo[1,2-*a*]quinoxalines in 82–92 % yields (Huang et al. 2011).

2.5.6 From 4-Bromo-5-nitrophthalonitrile

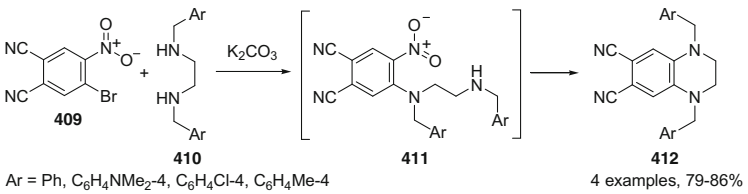
The strategy of building the pyrazine ring of the quinoxaline system is fundamentally different in the case of 4-bromo-5-nitrophthalonitrile **409**, with two nitrile groups which activate the other substituents on the benzene ring toward the nucleophilic aromatic substitution.

For example, the intermolecular nucleophilic substitution reaction of the halogen atom starts with the attack by one of the amino groups of the nucleophile **410** on the carbon atom of compound **409** which directly bears the bromine atom. The intermediate formed **411** contains simultaneously a nitro group and a nucleophilic center is active for further substitution. This second nucleophile then takes part in an intramolecular substitution reaction of the nitro group and this leads to the ring substitution and to the products **412** (Scheme 2.74) (Abramov et al. 2002).

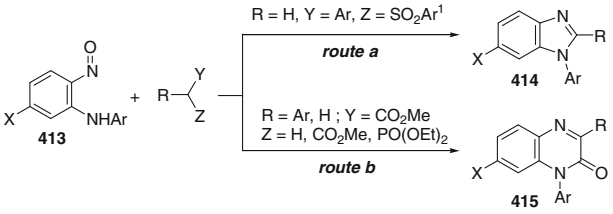
2.5.7 From N-Aryl-2-nitrosoanilines and Alkylated Cyanoacetic Esters

The vicinal position of nucleophilic amino and strongly electrophilic nitroso groups makes *N*-aryl-2-nitrosoanilines **413** (Wrobel and Kwast 2007, 2010) very interesting starting materials for domino reactions with properly equipped dipolar partners, leading to a variety of heterocyclic systems. The reactions of these compounds with comparatively acidic sulfones (Scheme 2.75, route *a*) or acetates and phosphonoacetates (Scheme 2.75, route *b*) appeared to be efficient ways of the synthesis of benzimidazoles **414** (Wrobel et al. 2011) and quinoxalin-2(1*H*)-ones **415** (Wrobel et al. 2013).

Reactions of 2-nitrosoarylamines with carbon nucleophiles leading to quinoxalin-2(1*H*)-one *N*-oxides are mentioned in literature, but the reported examples are limited to a few intramolecular reactions of pyrimidine derivatives, easy to synthesize via the direct nitrosation of appropriate aminopyrimidines (Pachter et al. 1963; Steinlin et al. 2008; Steinlin and Vasella 2009). Because carbocyclic *o*-nitrosoanilines were not so easily available, the common synthesis of

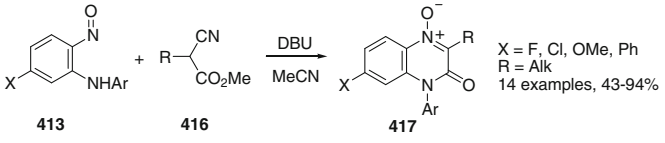


Scheme 2.74 Synthesis of *N*,*N*′-dialkylated tetrahydroquinoxalines **412** by the reaction of 4-bromo-5-nitrophthalonitrile **409** with secondary diamines **410**

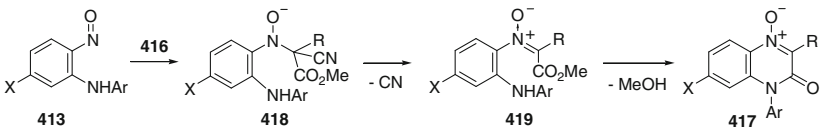


Scheme 2.75 The reaction of *N*-aryl-2-nitrosoanilines with sulfones (route *a*), acetates (route *b*) and phosphonoacetates (route *b*)

carbocyclic quinoxalin-2(1*H*)-one *N*-oxides was based on the Tennant intramolecular condensation of substituted *o*-nitroanilines with carbanions, in which a nitrone intermediate was formed (Sakata et al. 1985; Takano et al. 2003, 2005). Other synthetic approaches applied furoxanes (Ley and Seng 1975; Monge et al. 1977) or dioximes (Abushanab 1970, 1973; Duda et al. 2009) as starting materials. Simple oxidation of quinoxalin-2(1*H*)-ones was also frequently used (Clark-Lewis 1957; Toman and Klicnar 1984; Sakata and Makino 1984; Cazaux et al. 1993) in the synthesis of their *N*-oxides. A variety of these compounds were synthesized via an interesting reaction of anilines with 1,2,2-trichloronitroethene (Meyer et al. 2008). A later approach introduces the nitrone group together with two lacking carbon atoms in the ring-forming process. *N*-(2,6-Dimethylphenyl)-5-chloro-2-nitrosoaniline **413a** (X = Cl, Ar = C_6H_3-di-Me-2,6) smoothly reacted with diethyl *n*-butylcyanoacetate in the presence of DBU in acetonitrile at the room temperature furnishing 3-butyl-7-chloro-1-(2,6-dimethylphenyl)quinoxalin-2(1*H*)-one 4-oxide **417a** (X = Cl, Ar = C_6H_3-di-Me-2,6, R = *n*-Bu) in a 94 % yield (Scheme 2.76) (Krolikiewicz and Wrobel 2014). The reaction was completed within 15 min. Numerous nitrosoanilines substituted in *para*-position to the nitroso group with Cl, F, Ph, and OMe reacted in the same way. Changes in *N*-aryl substituent in 2-nitroso-*N*-arylamine seem to have only a small or no impact on the reaction course. The aryl group Ar can be both a carbocyclic ring with various substituents such as alkyl, alkoxyl, halogen, as well as a heterocyclic system. Bulky alkyl group in the cyanoacetic ester moiety (*i*-Pr versus Et or *n*-Bu) only slightly



Scheme 2.76 Synthesis of quinoxalin-2(1*H*)-one *N*-oxides **417** from *N*-aryl-2-nitrosoanilines **413**



Scheme 2.77 Plausible mechanism for the formation of quinoxalin-2(1*H*)-one 4-oxide

lowered the reaction rate. DBU/MeCN was the system of choice, but in some cases, the K_2CO_3/DMF system, despite a longer reaction time, gave better yields of the products (Krolikiewicz and Wrobel 2014).

The reaction proceeds via the initial addition of the carbanion to the nitrogen of the nitroso group followed by the elimination of the cyanide anion from the adduct **418** to form nitrone **419** (Scheme 2.77). The subsequent intramolecular acylation of the amine function, probably in the deprotonated form of **419**, provides quinoxalinone **417**. The formation of the nitrone moiety is probably analogous to the known reactions of the carbanions-bearing leaving groups such as diazo (Baldwin et al. 1969), sulfonium (Johnson 1963; Hamer and Macaluso 1964), pyridinium (Krohnke 1963; Nace and Nelander 1964), sulfonyl (Johnson 1963), or nitro (Lypkalo et al. 1996) with nitrosoarenes. It should be pointed out that the cyano group has been reported to act in this manner only in a few cases (Aurich 1965; Jawdosiuk et al. 1971; Makosza et al. 1974), and no one was engaged in intramolecular formation of a heterocyclic ring.

Thus, a new simple, convenient, and general method of the synthesis of various quinoxalin-2-one *N*-oxides was presented. The synthesis started from easily accessible substrates, that is, alkyl cyanoacetic esters and 2-nitroso-N-arylanilines which can be prepared from appropriate nitroarenes and anilines. Diversity of the compounds can be achieved by simply varying the substituents in each reagent.

2.6 Synthesis of Quinoxalines from Heterocyclic Systems

The methods for the synthesis of quinoxalines from various heterocyclic compounds can be divided into three groups: those based on various fused nitrogen-containing heterocycles without a pyrazine fragment, e.g., benzofuroxan, benzimidazole, azabicyclo[4.1.0]heptane and benzodiazepine; those based on various heterocyclic systems, which contain neither a pyrazine ring nor a benzofragment in their composition, *e.g.*, epoxide, azirine, pyrrolidin-3-one, piperidin-3-one, furanone, pyrandione, chromene, thiazolidine, selenazolidine, alloxan, and pyran-naphthoquinone; and those based on heterocyclic systems containing a pyrazine ring in their composition, e.g., pyrazine and quinoxaline.

2.6.1 *Synthesis of Quinoxalines from Various Fused Nitrogen-Containing Heterocycles Without a Pyrazine Fragment*

2.6.1.1 From Benzofuroxan and Various Suppliers of the Two-Carbon C(2)–C(3) Fragment

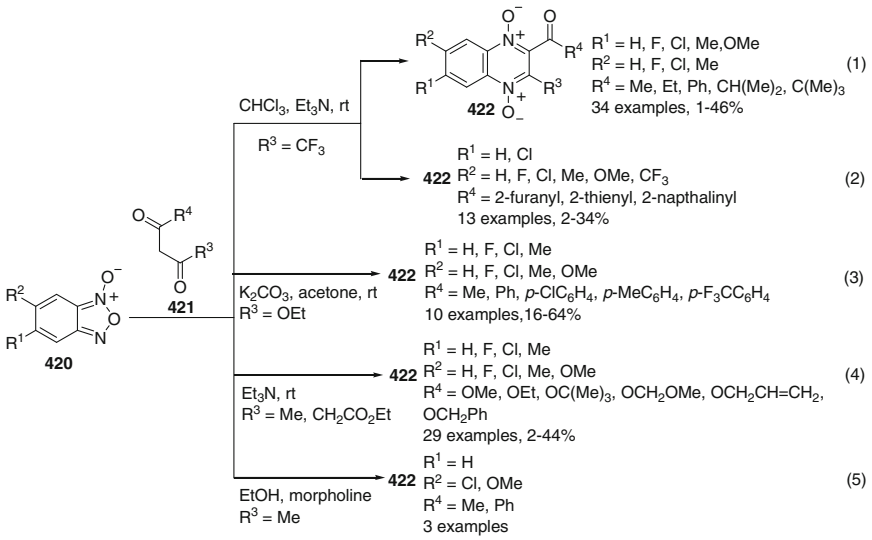
In this category, a leading place belongs to the cycloaddition reaction of benzofuroxan (benzofurazan *N*-oxide) with various suppliers of the two-carbon fragment C(2)–C(3) of the future quinoxaline (the Beirut reaction) (Laursen and Nielsen 2004). Mainly ketones (Chupakhin et al. 1999; Sun et al. 2011), β-diketones (Issidorides and Haddadin 1966; Haddadin et al. 1971; Xu et al. 2011b), β-ketoesters (Issidorides and Haddadin 1966), β-ketonitriles (Monge et al. 1995b; Hu et al. 2012), β-ketoamides (Haddadin and Issidorides 1976), and 1,3-dinitriles (Monge et al. 1995b; Cerecetto et al. 1999; Barea et al. 2011) are used as the suppliers of the two-carbon fragment. The reactions are carried out with weak bases as catalysts.

In addition, phenols, resorcinols, hydroquinones, or benzoquinones also undergo a similar dehydrative condensation (e.g., $NaOH/H_2O$, H_2O, $MeOH/RNH_2$, SiO_2/MeCN), with benzofuroxan under mild conditions, to give phenazine *N*,*N*′-dioxide derivatives (Laursen and Nielsen 2004). The Beirut reaction of unsymmetrically monosubstituted benzofuroxans proceeds with the formation of two regioisomers (Haddadin et al. 1971; Monge et al. 1995b). However, only one regioisomer is often obtained after the purification process (Monge et al. 1995b) as shown by the reaction between 5-substituted benzofuroxans with benzoylacetonitriles which gives only 7-substituted quinoxaline 1,4-dioxides (Mason and Tennant 1971). The high regioselectivity of the Beirut reaction is probably due to the fact that the substituents in benzofuroxans do not directly affect the formation of the quinoxaline 1,4-dioxides (Haddadin et al. 1971).

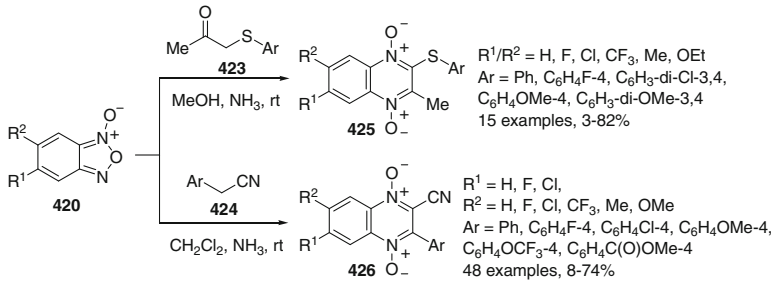
The Beirut reaction allows the introduction of any substituent at almost any position of a quinoxaline 1,4-dioxide, depending on the structures of the benzofuroxan **420** and the two-carbon unit (Scheme 2.78, Eq. 1) (Zarranz et al. 2004), (Scheme 2.78, Eq. 2) (Marin et al. 2008), (Scheme 2.78, Eq. 3) (Vicente et al. 2008; Romeiro et al. 2009), (Scheme 2.78, Eq. 4) (Jaso et al. 2005), (Scheme 2.78, Eq. 5) (Amin et al. 2006). Examples of reactions supporting this assertion are given in Scheme 2.76.

The use of acetonylphenyl sulfide **423** (Carta et al. 2002, 2004) and arylacetonitrile **424** (Scheme 2.79) (Vicente et al. 2008) instead of the usual ketones, as *C*-nucleophilic reagents, allows the introduction of appropriate substituents at C(2) of quinoxaline 1,4-dioxides **425**, **426**.

In 2011, Haddadin and coworkers reported that the Beirut reaction of a number of benzofurazan oxides **420** with 2-nitrobenzylcyanides **427** in acetonitrile with pyrrolidine as a catalyst, at room temperature, gave the corresponding 2-amino-3-(2-nitrophenyl)quinoxaline 1,4-dioxide **428**. It was surprising to find out that the



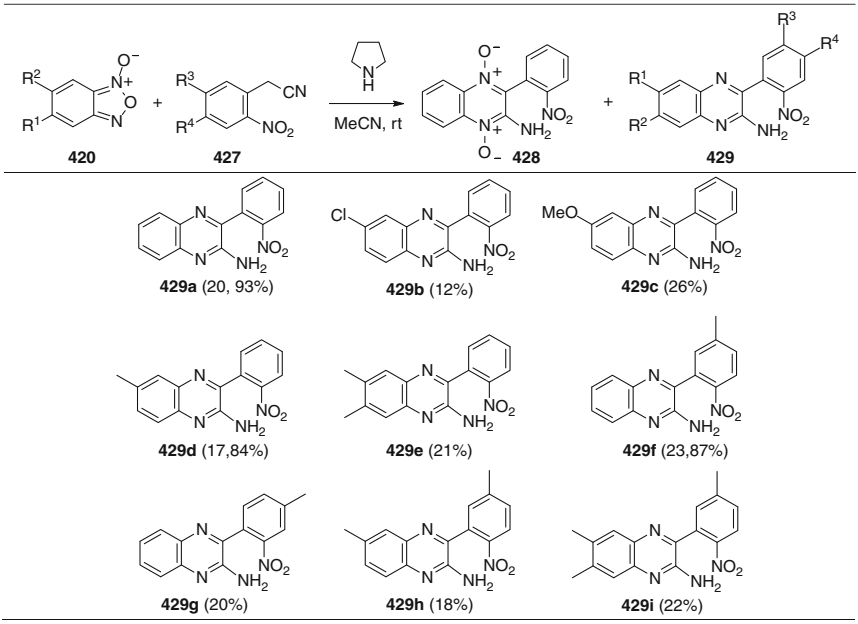
Scheme 2.78 Synthesis of 3-trifluoromethyl/alkoxy/alkyl/alkyloxycarbonyl/and 2-benzoyl/aroyl/alkanoyl/hetaroyl-quinoxaline 1,4-dioxide derivatives **422**



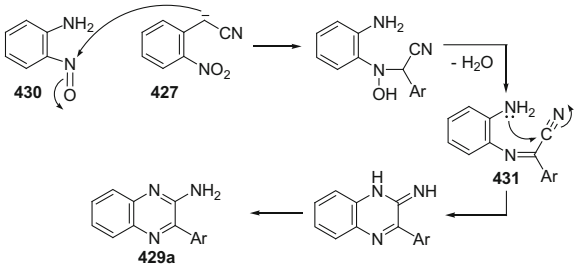
Scheme 2.79 Synthesis of 3-methyl-2-arylthioquinoxaline and 3-arylquinoxaline-2-carbonitrile 1,4-dioxides **425** and **426**

second product of this reaction, formed in almost equivalent amount, was the deoxygenated 2-amino-3-(2-nitrophenyl)quinoxalines **429** (Scheme 2.80) (Haddadin et al. 2011).

The possibility that the unusual quinoxaline **429a** could have arisen from deoxygenation of the quinoxaline 1,4-dioxide **428** was dismissed when it was found out that **428**, when subjected to these reaction conditions, remained unchanged even after one week. Mechanistic considerations led the authors to speculate that the formation of quinoxaline **429a** was due to the generation of 2-nitrosoaniline **430** which, in turn, reacted with 2-nitrobenzylcyanide **427** to give 2-amino-3-(2-nitrophenyl)quinoxalines (Scheme 2.81).



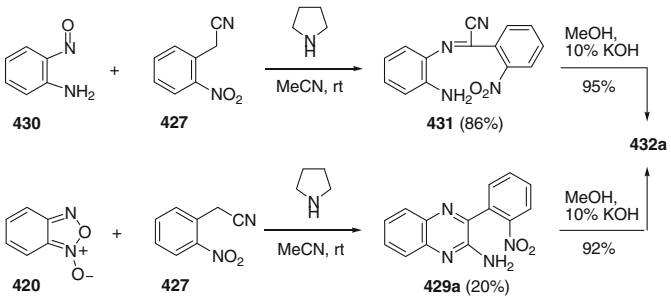
Scheme 2.80 Beirut reaction to quinoxaline derivatives



Scheme 2.81 Plausible mechanism for the formation of 2-amino-3-(2-nitrophenyl) quinoxaline **429a**

Indeed, the mother liquor from **420** + **427** showed the presence of trace amounts of 2-nitrosoaniline **430**, the identity of which was confirmed by comparison with an authentic sample. Furthermore, the reaction of independently prepared 2-nitrosoaniline **430** (Haddadin et al. 1979; Melnikov et al. 1992) with 2-nitrobenzyl cyanide, under the same reaction conditions (Scheme 2.82), yielded quinoxaline 6a in high yield. The postulated mechanism is supported by the fact that the reaction of 2-nitrosoaniline with cyanide **427** gave intermediate **431** as a deep red solid. Upon heating in 10 % methanolic KOH, **431** gave quinoxaline **429a**.

This easy formation of a series of 2-amino-3-(2-nitrophenyl)quinoxalines **429a**–**c**, **g** prompted the authors (Haddadin et al. 2011) to investigate their cyclization to the novel corresponding quioxalino[2,3-*c*]cinnoline 5-oxides **432a**–**d**, **h**. Indeed, this type of cyclization to form cinnoline *N*-oxides is well known (Haider and

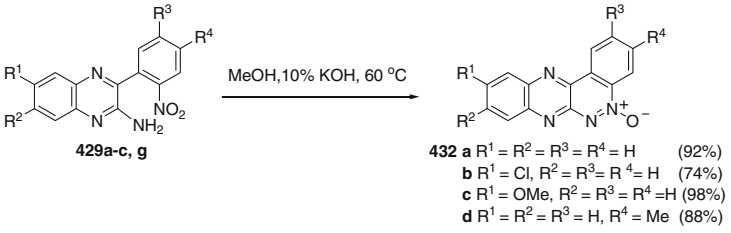


Scheme 2.82 Independent route to quinoxaline **429a**

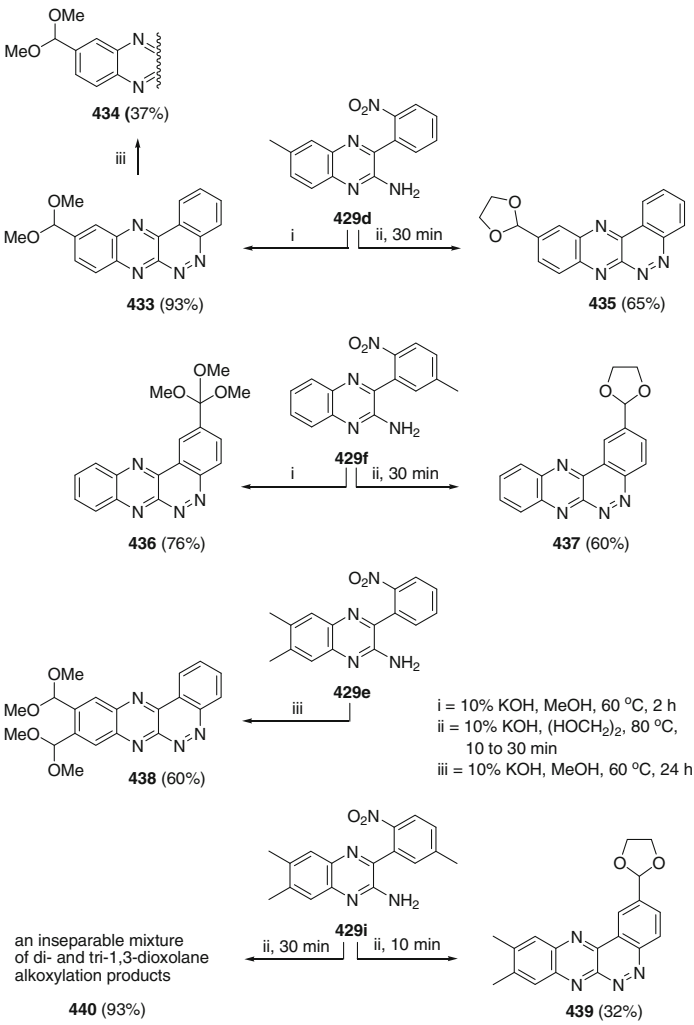
Holzer 2004). When heated methanolic KOH solutions of quinoxalines **432a–c**, **g** gave novel quinoxalino[2,3-*c*]cinnoline 5-oxides **429a–c**, **g** in high yields (80–90 %). Smith and coworkers (Shepherd and Smith 1987; Glidewell et al. 1987) have published the work on the preparation and reactions of quinoxalino[2,3-*c*] cinnolines using a different method that proceeded in relatively low yields. They also reported the preparation of three quinoxalino[2,3-*c*]cinnoline 5-*N*-oxide derivatives, which did not include the parent ring system. They stated that these quinoxalinocinnoline 5-*N*-oxides were impure and obtained in small quantities which "precluded further work on these compounds." As outlined in Scheme 2.83, the preparation of the parent system **432a** and a number of derivatives proceeded via a new, simple, and efficient synthetic route.

It is also noteworthy that the methyl-substituted 2-aminoquinoxalines **429d–f**, **h**, **i** underwent cyclization and alkoxylation at the benzylic carbon with subsequent deoxygenation of the anticipated 5-*N*-oxide to yield an acetal, an orthoester (with methanol/10 % KOH), or a 1,3-dioxolane **433–438** (with ethylene glycol/10 % KOH) (Scheme 2.84). A postulated mechanism for its formation is presented in Scheme 2.85. In contrast, when **429i** was heated with ethylene glycol, under the same reaction conditions but for 10 min, alkoxylation occurred at the methyl carbon of the 2-nitrophenyl group to give **439**, whereas when the reaction was extended to 30 min, a di- and tri-1,3-dioxolane-containing mixture was obtained **440**.

It is intriguing to speculate whether the 5-*N*-oxide functionality is lost during or after the alkoxylation reaction (Scheme 2.84). The authors (Haddadin et al. 2011)



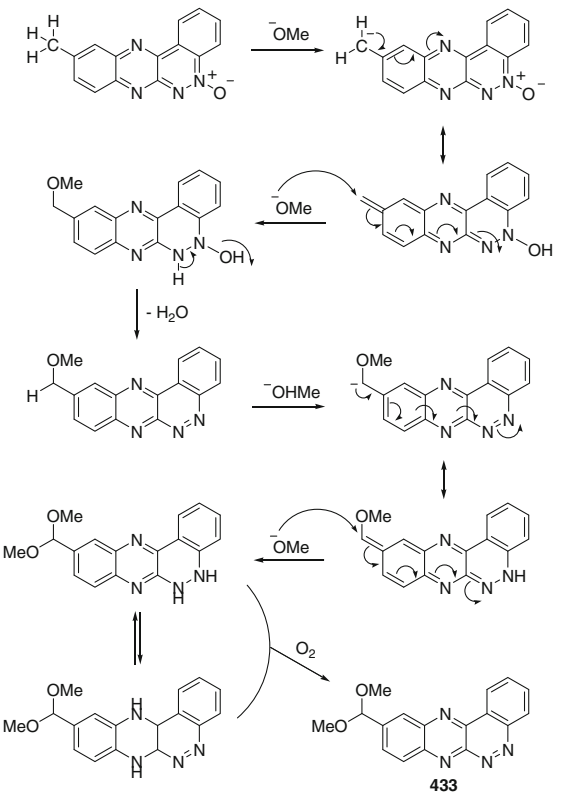
Scheme 2.83 Synthesis of quinoxalino[2,3-*c*]cinnoline 5-*N*-oxides



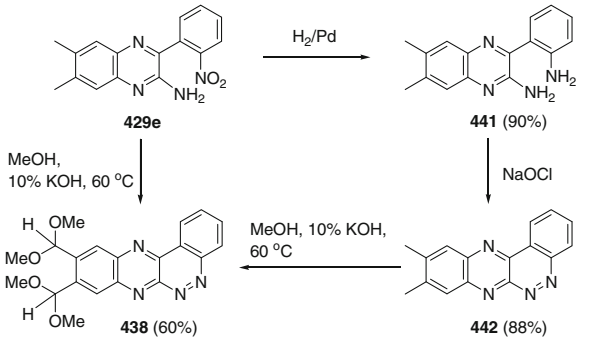
Scheme 2.84 Benzylic alkoxylation of methyl-substituted 2-aminoquioxalines

have no solid evidence to indicate at which step deoxygenation takes place. It is believed that this deoxygenation occurs during the alkoxylation reaction because the formation of quinoxalino[2,3-*c*]cinnoline **432a** and its further heating under cyclization conditions (10 % KOH/MeOH) did not result in deoxygenation. It is fascinating that the 5-*N*-oxide functionality does not appear to be essential for benzylic methoxylation. As outlined in Scheme 2.86, this assumption is supported by the fact that 9,10-dimethylquinoxalino-[2,3-*c*]cinnoline **442**, which was prepared by reduction (H_2/Pd) of 2-amino-3-(2-nitrophenyl)-4,5-dimethylquinoxaline **429e** followed by subsequent ring cyclization of **441** with Clorox, underwent

Scheme 2.85 Postulated mechanism for the formation of **433**



Scheme 2.86 Evidence that the 5-*N*-oxide moiety is not essential for benzylic alkoxylation



alkoxylation under the same conditions to give diacetal **438** in a high yield. It is interesting to note that the alkoxylation reaction proceeds well with primary alcohols, such as methanol, ethanol, or ethylene glycol in 10 % KOH, but fails with isopropyl or *tert*-butyl alcohols presumably because of its decreased nucleophilicity.

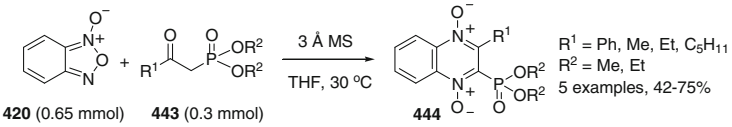
Thus, a new route for the Beirut reaction is revealed in which a number of novel 2-amino-3-(2-nitrophenyl)quinoxalines, in addition to their expected 1,4-dioxides, can be easily prepared and converted into novel quinoxalino[2,3-*c*]cinnoline 5-*N*-oxide which are rare in literature. In these investigations the curious fact is the fortuitous finding that the methyl substituents of some of quinoxalino[2,3-*c*]cinnolines, or their presumed 5-*N*-oxides intermediates, can be easily converted into acetals or orthoesters which we believe to be unprecedented.

An extension of the Beirut reaction for the preparation of the first members of the 2-phosphonylated quinoxaline 1,4-dioxide series has been described (Dahbi et al. 2010). Contrary to their carboxylated equivalents, preparation of these new compounds could not be achieved under basic conditions but required the use of powdered molecular sieves (Scheme 2.87). Good and reproducible yields were obtained only when the initial suspension in THF was transformed into a pasty film by the slow evaporation of ca. 90 % of the initial solvent volume.

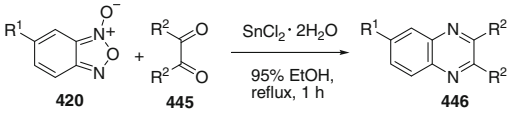
When α-dicarbonyl compounds are used instead of the usual enolizable ketones and β-carbonyl compounds, the benzofuroxans under reduction conditions (in the presence of stannous chloride $SnCl_2 \cdot 2H_2O$) behave as 1,2-DABs and form quinoxalines (Scheme 2.88) (Shi et al. 2008).

2.6.1.2 From Benzimidazole Derivatives

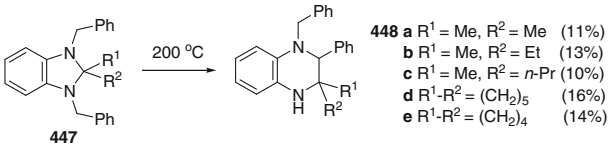
Benzimidazole, like benzofuroxan, containing two nitrogen atoms at positions 1 and 3 of the five-membered ring, can also serve as the initial reagent in quinoxaline synthesis. Thermolysis of 2,2-dialkyldihydrobenzimidazoles **447** was accompanied by their rearrangement into isomeric tetrahydroquinoxalines **448** in low yields (Scheme 2.89) (Reddy et al. 1996).



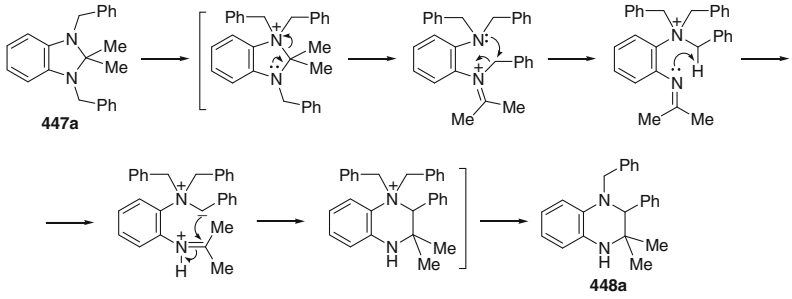
Scheme 2.87 The first successful Beirut reaction with dialkyl 2-oxopropylphosphonates



Scheme 2.88 The synthesis of quinoxalines **446** by the reaction of benzofuroxans **420** and 1,2-dicarbonyl compounds **446** mediated by $SnCl_2 \cdot 2H_2O$



Scheme 2.89 The rearrangement of 2,2-dialkyl-1,3-dibenzyl-2,3-dihydrobenzimidazoles **447** to the isomeric 1-benzyl-3,3-dialkyl-2-phenyl-1,2,3,4-tetrahydroquinoxalines **448**



Scheme 2.90 One of the more attractive mechanisms of the rearrangement

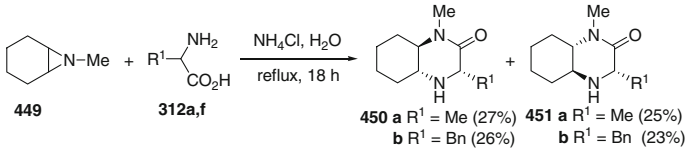
The authors proposed a possible mechanism for this reaction (shown with the dimethyl derivative as an example) (Scheme 2.90) (Reddy et al. 1996). However, they did not discuss what had happened to the molecule which provides the benzyl cation required in the first step. It should be noted that the formation of the final product can be represented as the thermal isomerization of benzimidazole to quinoxaline without participation of a benzyl cation.

2.6.1.3 From Azabicyclo[4.1.0]heptane

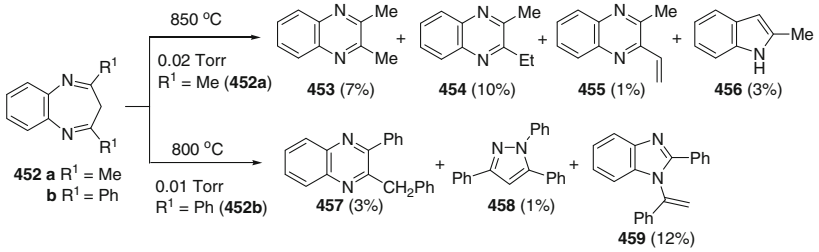
A quinoxaline-related system can emerge upon the expansion not only of a five- but also a three-membered heterocycle. New *trans*-perhydroquinoxalin-2(1*H*)-ones were prepared by the reaction of aziridines **449** with α-amino acids **312a**, **f** as a result of the aziridine ring cleavage and pyrazine ring formation (Scheme 2.91) (Rees 1987). Note that the reaction is non-stereoselective and gives a mixture of products **450** and **451**.

2.6.1.4 From Benzodiazepine Derivatives

A quinoxaline ring can be obtained not only with the small ring expansion but also by a medium ring contraction.



Scheme 2.91 Synthesis of *trans*-perhydroquinoxalin-2(1*H*)-ones



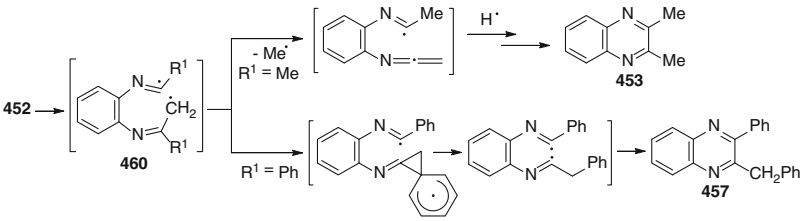
Scheme 2.92 Gas-phase pyrolysis of the 2,4-dimethyl- and 2,4-diphenyl-1,5-benzodiazepines **244a** and **244b**

The gas-phase pyrolysis of the 2,4-dimethyl- and 2,4-diphenyl-1,5-benzodiazepines **452a** and **452b** at 800–850 °C proceeds with the formation of a range of heterocyclic products (e.g, quinoxalines **453**–**455** and **457**, indole **456**, benzimidazole **459,** and pyrazole **458**) in low yields (Scheme 2.92) (Despinoy et al. 1998).

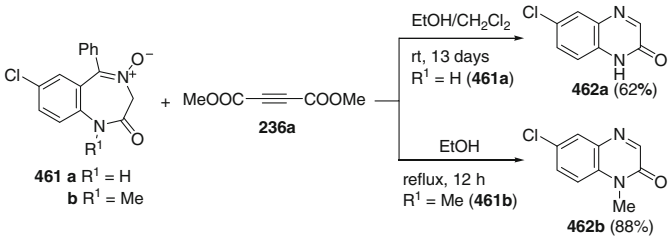
The authors suggest (Despinoy et al. 1998) that the formation of products results from homolytic cleavage of the C(2)–C(3) bond of the benzodiazepine to give an imidolyl-aza-allyl biradical pair **460**. The formation of quinoxaline **457** (3 %) requires a 1,2-phenyl shift in the aza-allyl unit, which may occur via a neophyl-type rearrangement (Cadogan et al. 1986) as shown in Scheme 2.93. The neophyl mechanism cannot account for the formation of 2-methyl-3-ethylquinoxaline **454** (10 %) from the dimethylbenzodiazepine **452a**, in which a formal 1,2-shift of the methyl group from the initial intermediate is required. The trace of vinyl compound **455** may be derived from **454** by thermal dehydrogenation. Formation of dimethylquinoxaline **453** clearly involves the loss of a C_1 unit, and there are a number of possibilities for this, including β-cleavage from biradical **460** (Scheme 2.93) (Despinoy et al. 1998).

1,4-Benzodiazepine derivatives react with 1,3-dipolarophiles, also with rearrangement, giving rise to quinoxalines in high yields. Thus *N*-oxide **461b** undergoes a 1,3-dipolar cycloaddition to dimethyl acetylenedicarboxylate **236a** in boiling ethanol for 12 h being converted into quinoxaline **462b** (Scheme 2.94) rather than into isoxazolidinobenzodiazepine **463b** (Scheme 2.94) (Miyadera et al. 1977).

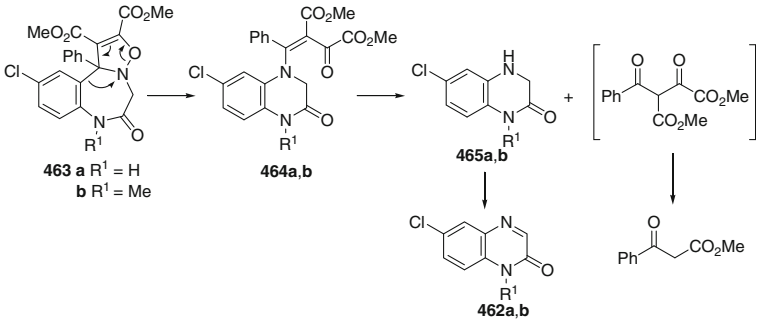
The authors assumed that under the reaction conditions, the adducts **463** were formed in the 1,3-cycloaddition, but then undergo a Beckmann-type rearrangement



Scheme 2.93 A possible mechanism for the formation of quinoxalines **453** and **457**



Scheme 2.94 Reactions of chlorodiazepam *N*-oxides **461** with DMAD **236a**



Scheme 2.95 A plausible mechanism for the formation of 6-chloroquinoxalin-2(1*H*)-ones **462a**, **b**

463 → **464** to give quinoxalines **462**, **465** (Scheme 2.95). Under mild conditions (stirring in Et_2O and CH_2Cl_2 at room temperature for three days), adducts **463** and the rearrangement product **464** with the same molecular formula were obtained in good yields. The latter compound is also produced on brief heating of the adduct in ethanol. After longer heating in ethanol, both intermediates are converted into quinoxaline with the evolution of methyl and ethyl benzoylacetates (detected by chromatography).

2.6.2 *Synthesis of Quinoxalines from Various Heterocyclic Systems, Containing Neither a Pyrazine ring nor a Benzofragment*

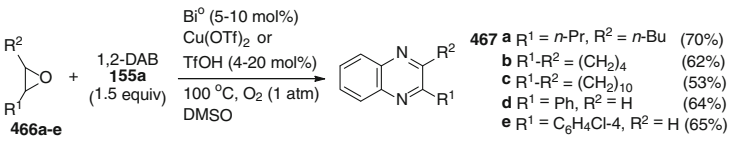
2.6.2.1 From Epoxides

A new strategy allows preparation of differently substituted quinoxalines directly from simple epoxides and diaminoaryl compounds, in an oxidative coupling catalyzed by bismuth powder (Antoniotti and Duñach 2002). The reaction proceeds in DMSO under molecular oxygen in the presence of catalytic amounts of Bi(0) powder and with copper triflate or triflic acid as additives.

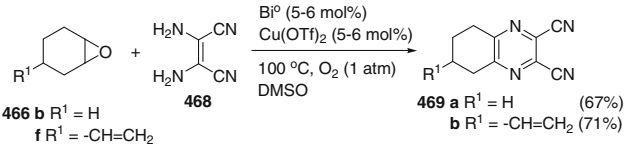
The synthesis of 2,3-disubstituted quinoxalines **467a–c** was achieved in yields of 53–70 % using 1,2-DAB **155a** and internal epoxides **466a–c** (R^1 = *n*-Pr, R^2 = *n*-Bu; R^1–R^2 = $(CH_2)_4$ and R^1–R^2 = $(CH_2)_{10}$) (Scheme 2.96). The oxidative coupling of 1,2-DAB **155a** and monosubstituted styrene oxide derivatives **466d,e** (R^1 = Ph, R^2 = H and R^1 = C_6H_4Cl-4, R^2 = H) afforded 2-arylquinoxalines **467d**, **e** in 64–65 % yields (Scheme 2.96) (Antoniotti and Duñach 2002).

The replacement of 1,2-DAB **155a** by 2,3-diaminomaleonitrile **468** in the reaction with cyclohexene oxides **466b**, **d** led to the tetrahydroquinoxaline derivatives **469**, according to Scheme 2.97 (Antoniotti and Duñach 2002).

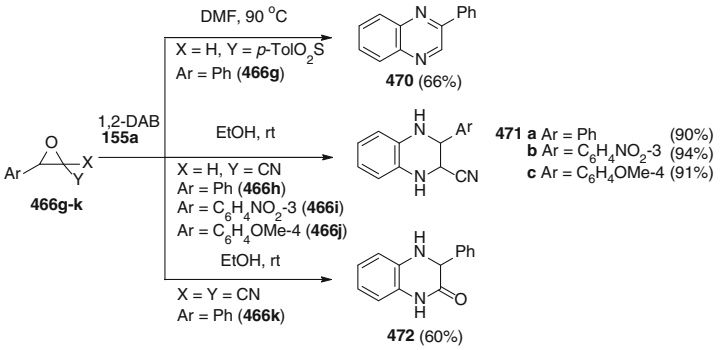
For the mechanistic aspects of this new transformation, a first oxidation of the epoxide to the corresponding α-hydroxyketone and its further oxidation to the α-diketone have been proposed in agreement with the results in this field (Antoniotti and Duñach 2001). This oxidation proceeds by the oxidative ring opening of the oxirane by DMSO (Santosusso and Swern 1975), catalyzed by an acidic additive,



Scheme 2.96 Synthesis of 2,3-susbstituted quinoxaline derivatives **467** from epoxides **466** and 1,2-DAB **155a**



Scheme 2.97 Synthesis of tetrahydroquinoxaline derivatives **469** from cyclohexene oxides **466b**, **f** and 2,3-diaminomaleonitrile **468**



Scheme 2.98 Synthesis of 2-phenyl/2-aryl-3-cyano- and 3-phenyl-2-oxo-quinoxalines **470**, **471,** and **472**

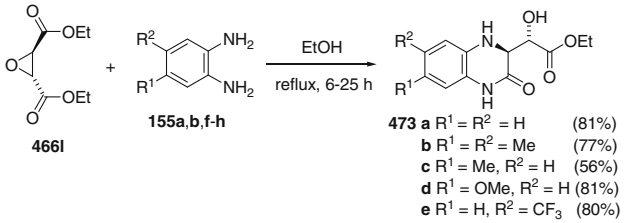
leading to the corresponding α-hydroxyketone or α-hydroxyaldehyde. In the second step, the ketol (or ketal) is oxidized to the α-diketone or to the α-ketoaldehyde intermediates according to Bi(0)/O_2 system, in a Bi(III)/Bi(0) redox process (Coin et al. 2001). The in situ α-dicarbonyl compound obtained affords the corresponding quinoxaline after the double condensation/dehydration with the 1,2-diamino derivatives.

The condensation of 2-(*p*-tolylsulfonyl)-3-phenyloxirane **466g** with 1,2-DAB **155a** on heating in DMF furnishes 2-phenylquinoxaline **470** ina 66 % yield (Scheme 2.98) (Taylor et al. 1980). Apparently, phenylquinoxalines are formed upon the primary attack by the amino group on the C(3) carbon atom bearing the phenyl group with the oxirane ring opening; this is followed with the attack by the second amino group on the carbonyl group formed, and, finally, the oxidation of the 1,2-dihydro derivative (Taylor et al. 1980).

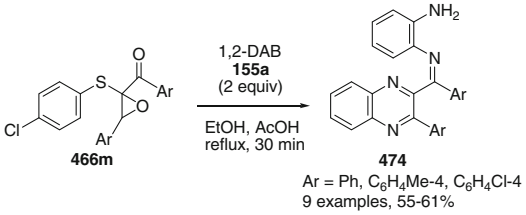
The application of this approach to 2-cyano- and 2,2-dicyano-3-aryloxiranes **466h–j** and **466k** led to 2-aryl-3-cyano- **471a–c** and 3-phenyl-2-oxo-1,2,3,4-tetrahydro- **472** quinoxalines, respectively (Scheme 2.98). They are dehydrogenated to give aromatic derivatives on heating in ethanol in the presence of mercuric oxide.

Diethyl (*R*,*R*)-oxirane-2,3-dicarboxylate was obtained from diethyl (2*R*, 3*R*)-(+)-tartrate with 1,2-DABs at elevated temperature under argon to give optically active tetrahydroquinoxalin-2-ones **473** in good yields (Scheme 2.99) (Woydowski et al. 1998). Note that for 1,2-DABs, and derivatives with electron-donating substituents, refluxing in ethanol is sufficient, whereas for 4-nitro-1,2-DAB, **155n**, heating without a solvent at 155 °C is required (Woydowski et al. 1998).

A series of new quinoxalines **474** were prepared in 55–61 % yields by the one-pot three-component condensation of epoxy ketones **466m** with 1,2-DAB **155a** in ethanol in the presence of catalytic amounts of AcOH (Scheme 2.100) (Nasar et al. 2007). The authors assumed that the reaction occurs as a tandem process comprising the following sequence of transformations: acid-catalyzed aminolysis of



Scheme 2.99 Synthesis of optically active α-hydroxy-α-(tetrahydroquinoxalin-3-on-2-yl)esters **266** by ring transformation of diethyl (*R*,*R*)-oxirane-2,3-dicarboxylate **466l**



Scheme 2.100 Three-component reaction of (2-arylsulfanyl-3-aryl-2-oxiranyl)(aryl)methanones **466m** with 1,2-DAB **155a** in the presence of a catalytic amount of AcOH

oxirane, cyclization, elimination of benzenethiol, oxidation with air oxygen, and condensation of the resulting aroylquinoxaline with the second 1,2-DAB molecule. The formation of the product even with the 1:1 reactant ratio shows that aroylquinoxaline is highly reactive and undergoes further condensation, resulting in imine. This might be due to the protonation of the carbonyl carbon atom or the quinoxaline nitrogen atom with acetic acid, which increases the electrophilicity of the carbonyl function.

As noted above (see Sect. 2.2.5), the reaction of chloroarylpyruvates **156e** (Ar = $C_6H_4NO_2$-4) with 1,2-DAB **155a** affords quinoxalin-2(1*H*)-ones **226** (Mamedov et al. 1989).

The chloro ketones used in these reactions are obtained by the isomerisation of chloro epoxides. However, chloro epoxide **466n** (unlike isomeric chloro ketone **156e)** (Mamedov et al. 1989) condenses with 1,2-DAB **155a** to give quinoxaline **475** (Scheme 2.101) (Mamedov et al. 1994).

Scheme 2.101 Synthesis of 2-methoxycarbonyl-3-(3-nitrophenyl)quinoxaline **475**

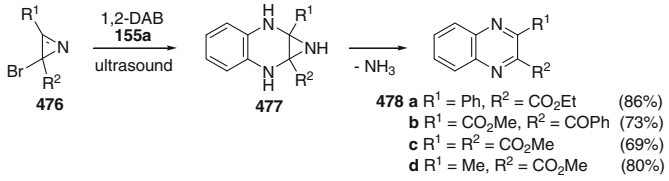
2.6.2.2 From Azirines

Quinoxalines **271a–d** were obtained in high yields when the reactions of azirines **476** with 1,2-DAB **155a** were carried out in an ultrasound bath (Scheme 2.102) (Pinho e Melo et al. 2002). In a process analogous to the one described for the synthesis of 1,2-diimines, 2*H*-azirines **476a** (R^1 = Ph, R^2 = CO_2Et), **476b** (R^1 = CO_2Me, R^2 = COPh), **476c** (R^1 = R^2 = CO_2Me), and **476d** (R^1 = Me, R^2 = CO_2Me) underwent halide displacement and addition to the iminic double bond on reacting with 1,2-DAB **155a**, with **477** as a result. The opening of the aziridine ring followed by the elimination of ammonia led to the quinoxalines **478** (Scheme 2.102) (Pinho e Melo et al. 2002). Attempts were made to promote the reaction of azirine **476a** with 1,2-DAB **155a** at room temperature and even at 65 °C, but there was no evidence of the expected product.

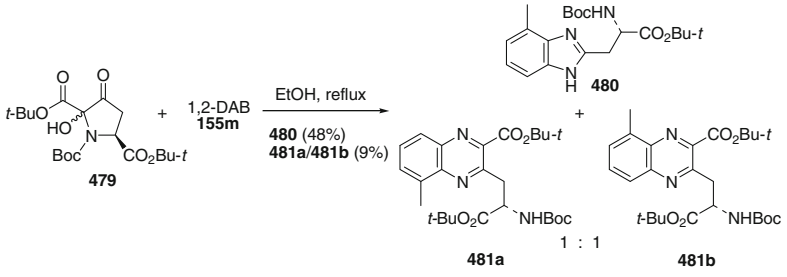
2.6.2.3 From Pyrrolidin-3-one and Piperidin-3-one

When a condensation of pyrrolidin-3-one **479** with 3-methyl-1,2-DAB **155m** was attempted in EtOH, a mixture of products was observed from which benzimidazole **480** could be isolated in a 48 % yield, along with a 9 % yield of the originally expected quinoxaline products **481a**, **b** (Scheme 2.103) (Adlington et al. 2001).

However, the reaction of pyrrolidin-3-one **479** with pyridine-2,3-diamine **482** which significantly alters the electronic nature and the nucleophilicity appeared



Scheme 2.102 Azirines as the suppliers of the C(2)–C(3) fragments for the construction of quinoxalines

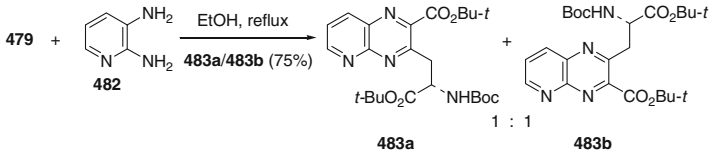


Scheme 2.103 Condensation of pyrrolidin-3-one **479** with 1,2-DAB **155m**

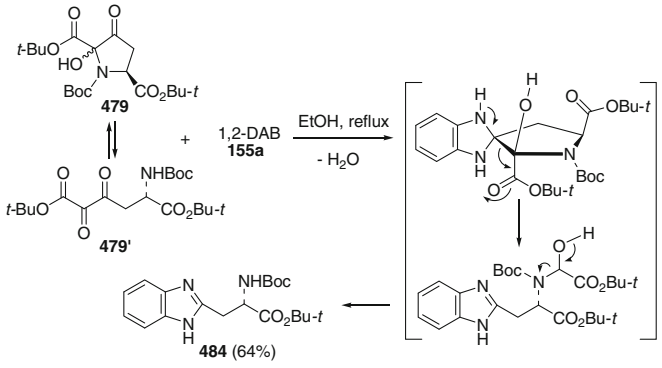
much cleaner than those above and allowed the formation of the expected quinoxaline products **483a** and **483b**, as an inseparable mixture of regioisomers in 75 % yield. No evidence of analogous benzimidazole-type products was observed (Scheme 2.104) (Adlington et al. 2001).

Various diamines had been shown to react with the reactive substrate **479** in different ways. In the condensation of 1,2-DABs **155a**, **m**, the major benzimidazolyl product is believed to be formed by a rapid condensation of the diamine upon the ketonic carbonyl of the cyclic species **479**. This reaction is encouraged by the high reactivity of 5-membered cyclic ketones toward the nucleophilic attack, to alleviate the ring strain. Aromatisation to the benzimidazole then causes ring opening with the subsequent elimination of oxoacetic acid *tert*-butyl ester to generate the observed products (Scheme 2.105) (Adlington et al. 2001).

Not withstanding the 1,2-DAB-derived benzimidazole products described above, the use of pyridine-2,3-diamine **482** did allow the desired pyrazine cyclocondensation to occur. It was postulated that this may be a combination of two factors, the first being the significantly reduced *N*-nucleophilicity of the 2-amino group. This would dramatically lower the rate of the secondary condensation with respect to other diamines, allowing the equilibrium ring opening mechanism to be more predominant. It was also suggested that the pyridine diamine may have a more direct effect on the equilibrium of ring opening. 2-Amino- and 2-hydroxypyridines are known to catalyze the ring opening of sugars to bring about mutarotation

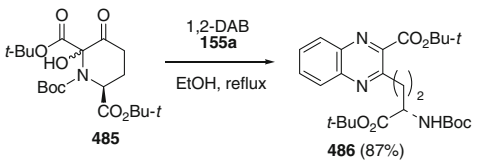


Scheme 2.104 Condensation of pyrrolidin-3-one **479** with pyridine-2,3-diamine **483**



Scheme 2.105 A plausible mechanism for the formation of the benzimidazole derivative **484**

Scheme 2.106 A condensation of piperidin-3-one **485** with 1,2-DAB **155a**



(Swain and Brown 1952). It was therefore proposed that the pyridine-2,3-diamine **482** may also behave as a catalyst for the ring opening of starting pyrrolidinone **479**. This would allow the pyrazine cyclocondensation to take place and the combination of both factors may explain the observed mixture of regioisomers (Adlington et al. 2001).

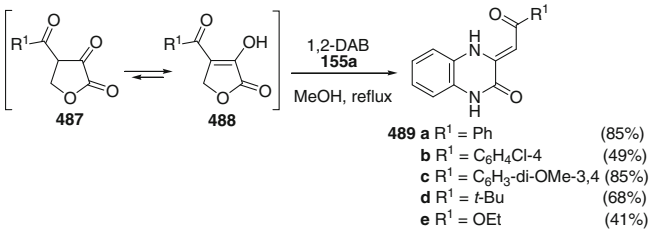
In order to compare the reactivity of piperidin-3-one **485** with its aspartate homologue **479** a reaction with 1,2-DAB **155a** was attempted. This resulted in the formation of the desired quinoxaline **486** in a very high yield (87 %), with no benzimidazole product being observed (Scheme 2.106) (Adlington et al. 2001).

2.6.2.4 From α-Keto-β-substituted γ-Butyrolactones (3-Hydroxyfuran-2(5*H*)-ones)

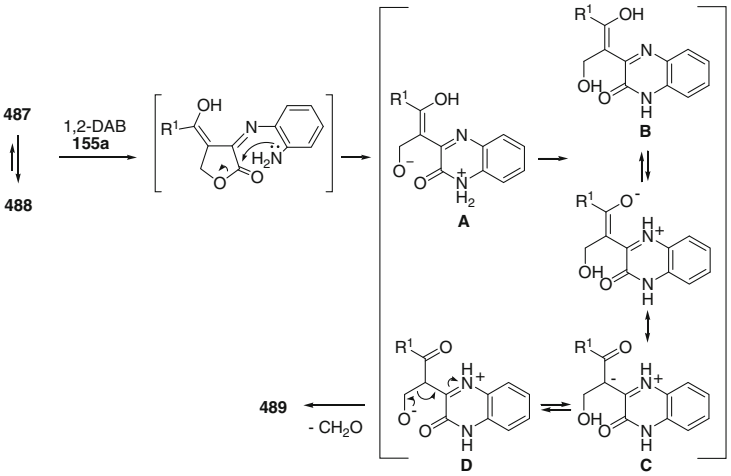
The condensation of α-keto-β-substituted γ-butyrolactones **487** (3-hydroxyfuran-2-(5*H*)-ones **488**) with 1,2-DAB **155a** results in 3-substituted 3,4-dihydroquinoxalin-2(1*H*)-ones **489** (Scheme 2.107) (Amer et al. 1983).

The authors assumed that the reaction starts with the nucleophilic attack by the amino group on the keto group of furanone to give the Schiff base. After that, attack by the second amino group on the lactone carbonyl group results in ring opening. The process is completed by a retro-aldol reaction with the evolution of formaldehyde (identified as a reaction product using dimedone) (Scheme 2.108) (Amer et al. 1983).

The reaction of α-keto-β,β-dimethyl γ-butyrolactone **490** with 1,2-DABs **155a**, **c** in water under mild conditions proceeds with the formation of 3-(2-hydroxy-1,1-dimethylethyl)quinoxalin-2(1*H*)-ones **491** (Scheme 2.109) (Murthy et al. 2010). The hydroxymethyl fragment is retained here, in contrast to the

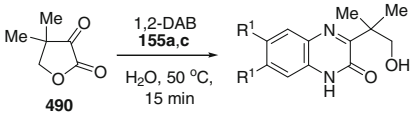


Scheme 2.107 Condensation of α-keto γ-butyrolactones **487** with 1,2-DAB **155a**



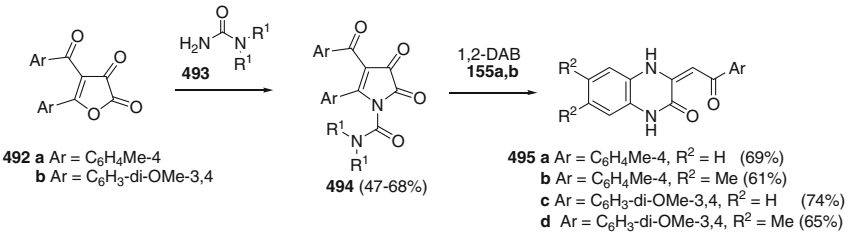
Scheme 2.108 A plausible mechanism for the formation of 3,4-dihydro-2(1*H*)-quinoxalinone **489** from 3-hydroxyfuran-2-(5*H*)-ones **487** ⇆ **488**

Scheme 2.109 Synthesis of 3-substituted quinoxalin-2(1*H*)-ones **491** in H_2O

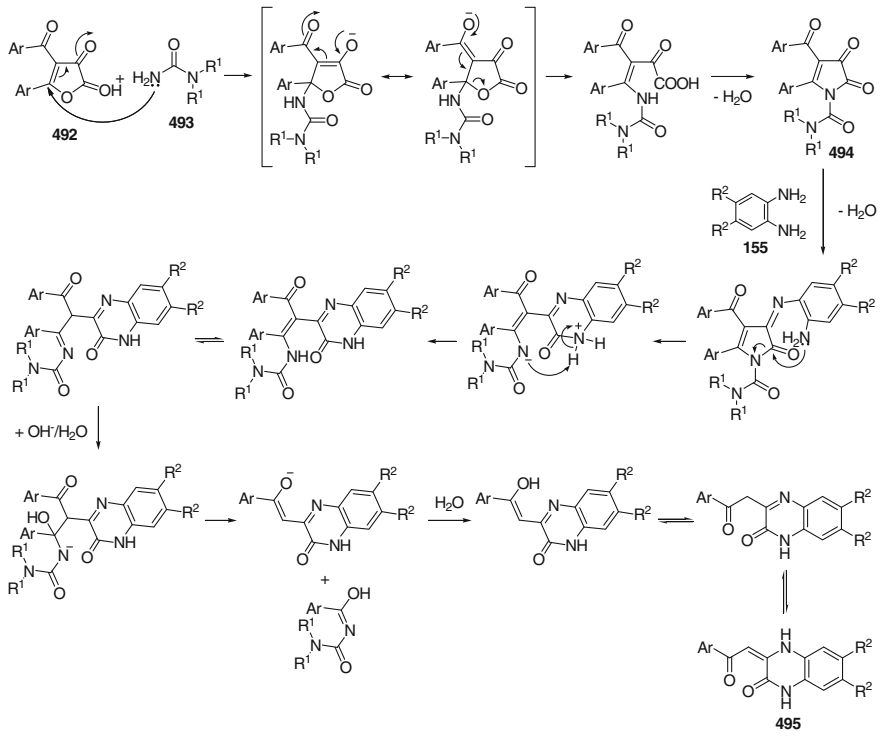


above-mentioned example, apparently due to the impossibility for the existence of different tautomeric forms such as **A**, **B**, **C,** and **D** (Scheme 2.108), due to the structural features of the original lactone **490**.

The 1*H*-pyrrole-2,3-diones **494** easily available from the reactions of 4-(4-methylbenzoyl)-5-(4-methylphenyl)-2,3-furandione **492a** and 4-(3,4-dimethoxybenzoyl)-5-(3,4-dimethoxyphenyl)-2,3-furandione **492b** with the *N*,*N*-disubstituted urea derivatives **493** were performed with 1,2-DABs **155a**, **b** and lead to 2(1*H*)-quinoxalinone derivatives **495** in 61–74 % yields (Koca and Yildirim 2012) (Scheme 2.110).



Scheme 2.110 Synthesis of pyrrol-2,3-diones **494** and their reaction with 1,2-DABs **155a**, **b**

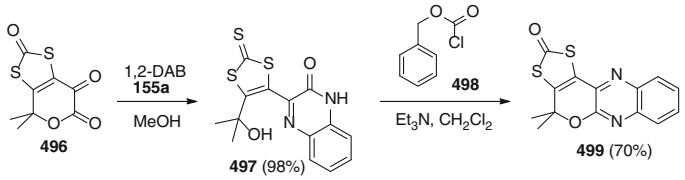


Scheme 2.111 Formation of pyrrol-2,3-diones **494** and quinoxalin-2-ones **495**

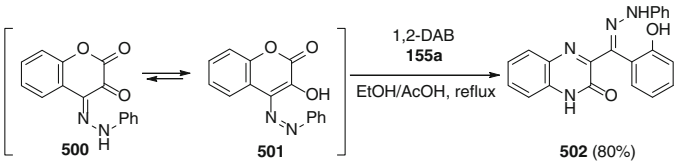
The mechanism of the formation of 1*H*-pyrrole-2,3-diones **494** involves first the Michael-type attack of nitrogen atom of NH_2 group of the urea derivative on C(5) in the furandione ring. Later, the molecule of water was eliminated and compound **494** was obtained. Nucleophilic addition of 1,2-DABs **155** to pyrrole-2,3-dione **494** lead to quinoxalin-2-ones **495**. These compounds arise from the sequential attacks of 1,2-DABs at the C(3) and C(2) atoms of pyrrolidine, respectively, followed by the elimination of water and pyrrole ring opening, and the basic hydrolysis of this intermediate provides the final product **495**. A possible reaction scenario is outlined in Scheme 2.111.

2.6.2.5 From Pyran-2,3-dione

The reaction of pyran-2,3-dione **496** with 1,2-DAB **155a** in MeOH afforded quinoxaline **497** almost quantitatively. The addition of benzyl chloroformate **498** and Et_3N to quinoxaline **497** leads to the formation of compound **499** in good yield (Scheme 2.112) (Marbella et al. 2009).



Scheme 2.112 Condensation of pyran-2,3-dione **496** with 1,2-DAB **155a**



Scheme 2.113 Condensation of chromane-2,3,4-trione 4-phenylhydrazone **500** with 1,2-DAB **155a**

2.6.2.6 From 2*H*-Chromene

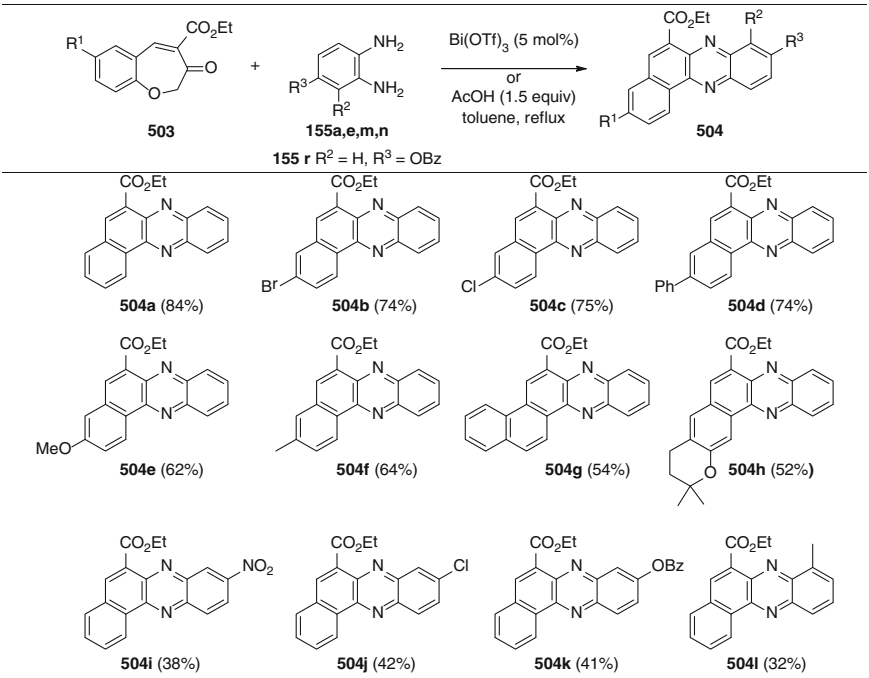
As an α-keto lactone, phenylhydrazone **500** (2*H*-chromene derivative) reacts with 1,2-DAB **155a** in a boiling EtOH/AcOH mixture, with ring cleavage giving rise to quinoxalin-2-(1*H*)-one **502** (Scheme 2.113) (Vinot et al. 1983).

2.6.2.7 From Benzoxepine-4-carboxylate

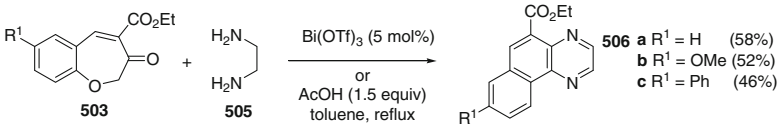
A new one-pot protocol has been developed for the synthesis of benzophenazine and quinoxaline derivatives by the reaction of benzoxepine-4-carboxylates with 1,2-DABs and ethane-1,2-diamine in the presence of $Bi(OTf)_3$ (5 mol%) under mild conditions in very good yields (Raju et al. 2014). The electron-withdrawing or electron-donating groups present on benzoxepine were well tolerated to produce **504b–h** in very good yields, whereas groups present on 1,2-DAB produced **504i–l** in moderate yields (Scheme 2.114).

To expand the scope of the present method, ethane-1,2-diamine **505** was examined. Under optimized conditions, **503a** (R^1 = H) was reacted with ethane-1,2-diamine **505** producing benzoquinoxaline-4-carboxylate **506a** in 58 % yield (Scheme 2.115). Phenyl and methoxy groups present on benzoxepine were well tolerated to produce **506b**, **c**.

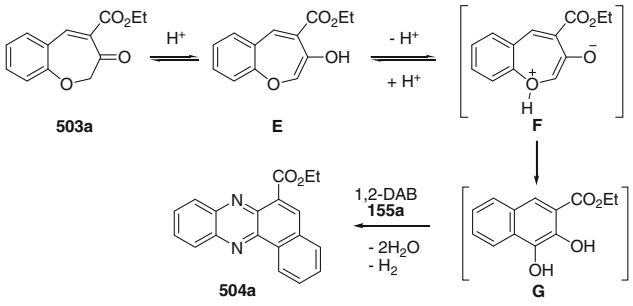
A proposed mechanism for this new reaction is shown in Scheme 2.116. Initially, the reaction was expected to involve enolization of benzoxepine **503a** to its corresponding enol derivative **E**. Protonation of intermediate A would then give oxonium ion **F**. Finally, the unstable oxonium ion **F** was rearranged by C–O bond



Scheme 2.114 Synthesis of benzophenazine-6-carboxylate derivatives **504**



Scheme 2.115 Synthesis of benzoquinoxaline-4-carboxylate derivatives **506**



Scheme 2.116 Proposed mechanism for phenazines **504**

cleavage to form a new C–C bond to give its corresponding ethyl 3,4-dihydroxy-2-naphthoate **G**. Condensation of ethyl 3,4-dihydroxy-2-naphthoate **G** with 1,2-DAB **155a** in situ provided phenazine derivative **504a**.

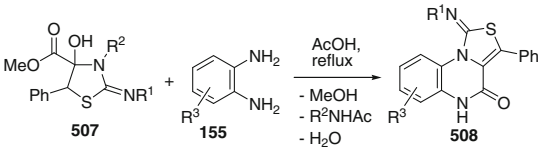
The method opens a new way for C–C, C–N, and C–O bond-formation reactions in a single-step process.

2.6.2.8 From 4-Hydroxythiazolidines

In all the above reactions, a variety of heterocyclic systems, acting as C_2 synthons, were utilized not only as structural components for quinoxalines, but also to introduce different substituents in positions 2 and (or) 3, depending on the source of the heterocycle. It has been recently shown that if 4-hydroxy-3,5-diphenyl-4-methoxycarbonyl-2-phenylthiazolidine **507a** ($R^1 = R^2 = Ph$)–a protected derivative of methyl phenylchloropyruvate **156e**–is used to supply the C_2 fragment, the reaction does not stop at the stage of the formation of the usual quinoxaline derivative (see Sect. 2.2.5), but proceeds further, to the formation of a fused derivative–1-phenylimino-3-phenylthiazolo[3,4-*a*]quinoxalin-4(5*H*)-one **508a** ($R^1 = Ph$, $R^3 = H$) in a 95 % yield (Scheme 2.117) (Mamedov and Levin 1996; Mamedov et al. 2004a, b).

It should be pointed out that before the discovery of this reaction, the synthetic possibilities of 4-hydroxythiazolidine derivatives were essentially limited to dehydration with the formation of corresponding thiazolines (Metzger 1978; Humplett and Lamon 1964a, b; Hanefeld and Wurtz 2000; Ge et al. 2004; Murav′eva and Schukina 1960), even though the first of their kind has been known for over a hundred years (Metzger 1978).

As can be seen from Scheme 2.117, 4-hydroxythiazolidine derivative **292** providing a five-atom fragment is almost fully utilized in the construction of **293**. It is noteworthy that varying the substituents in the 4-hydroxythiazolidine **292** in the isothiourea fragment (in exo- and endocyclic nitrogen atoms) makes it possible to obtain thiazolo[3,4-*a*]quinoxaline **293** with various substituents at position 1 (imine fragment). In its turn, 5-phenyl-4-hydroxythiazolidine **292** can be easily obtained by the reaction of the ester of 3-chloro-3-phenyl-2-oxopropanoic acids **156e** (Ar = Ph) with *N*-phenyl-*N*′-aryl(hetaryl)thiourea (Mamedov et al. 2004a, 2007).



Scheme 2.117 Synthesis of 1-aryl(hetaryl)imino-3-phenylthiazolo[3,4-*a*]quinoxalin-4(5*H*)-one **508**

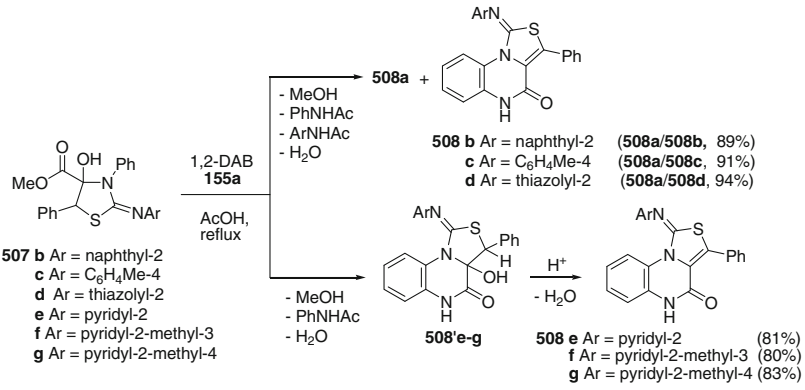
The section reveals the synthetic potential of this new reaction, not only for variously substituted thiazolo[3,4-*a*]quinoxalines but also for related new heterocyclic systems as well.

Reaction of unsymmetric 4-hydroxythiazolidines **507b–d** with the non-substituted 1,2-DAB **155a** led to the formation of a mixture of thiazolo[3,4-*a*] quinoxalines **508a** and **508b–d** (Scheme 2.118) (Mamedov et al. 2004a, b).

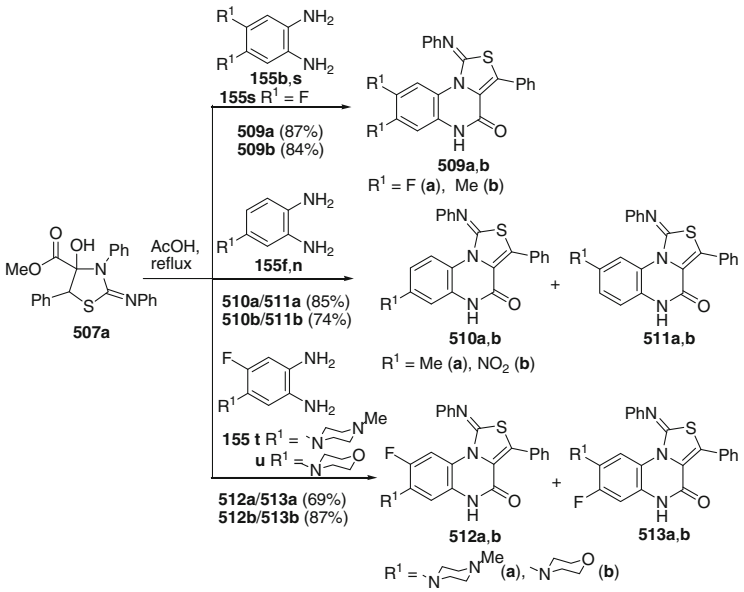
Reactions of 4-hydroxy-2-(*R*-pyridyl)iminothiazolidines **507e–g** with the non-substituted 1,2-DAB **155a** proceed with the formation of only 1-(*R*-pyridyl) iminosubstituted thiazolo[3,4-*a*]quinoxalines **508e–g** (Scheme 2.118). Thus during the condensation, the aniline and not 2-aminopyridine or 2-aminopicoline is eliminated (Mamedov et al. 2007, 2012). It may be noted that the presence of iminopyridyl and α(γ)picolyl groups in the composition of thiazolo[3,4-*a*]quinoxalines makes it possible, if necessary, to obtain water-soluble salts of this polycondensed system.

Under similar conditions and in contrast to their actions of thiazolidines **507b–d** with 1,2-DAB **155a**, which lead to the final product within 3–5 min, the reaction of *R*-pyridyl-containing thiazolidines **507e–g** with 1,2-DAB **155a** takes about an hour and this provides the opportunity to separate intermediate products. After boiling for five minutes, precipitation of crystals occurs which differ from the final product. In the example of the reaction of **507e,** we were able to show that this intermediate is the hydrate **508′e** (Pozharskii 1985) of the final product—thiazolo [3,4-*a*]quinoxaline **508e** (Scheme 2.118). The structure of the covalent hydrate **508′e** was established by IR and ^{1}H NMR spectroscopy and confirmed by X-ray analysis. On further boiling in acetic acid, the covalent hydrate **508′e** loses water and is converted into thiazolo[3,4-*a*]quinoxaline **508e** in almost quantitative yield (Scheme 2.118) (Mamedov et al. 2007).

When 4-mono- and 4,5-disubstituted 1,2-DAB derivatives are used instead of the non-substituted 1,2-DAB **155a** in the reaction with 4-hydroxythiazolidines **507**, 7,8-substituted thiazolo[3,4-*a*]quinoxalines can be obtained. In such a way the



Scheme 2.118 Reactions of unsymmetric 4-hydroxythiazolidines **508b–g** with1,2-DAB **155a**



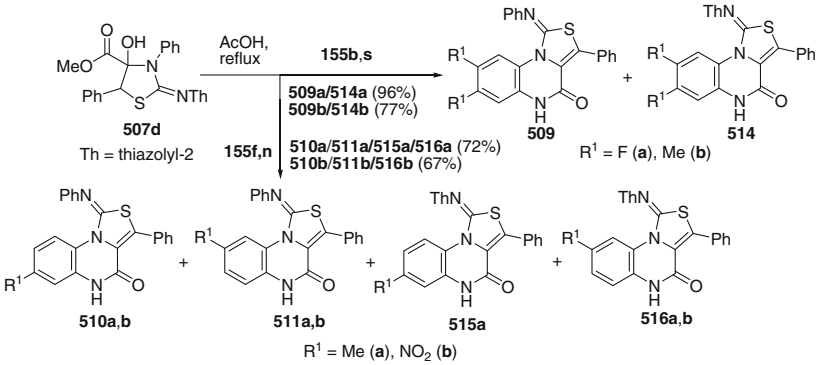
Scheme 2.119 The reactions of symmetrical 4-hydroxythiazolidine **507a** with the substituted 1,2-DABs **155b**, **f**, **n**, **s**–**u**

reactions of symmetrical 4-hydroxythiazolidine **507a** with symmetrically substituted 1,2-DABs **155b**, **n** result in the formation of 7,8-disubstituted thiazoloquinoxalines **509** (Mamedov et al. 2004a, b, 2009a, 2012), and with the unsymmetrically substituted 1,2-DABs **155f**, **n**, a mixture of two regioisomeric thiazoloquinoxalines **510** and **511** is obtained (Scheme 2.119) (Mamedov et al. 2004a, b, 2009a, 2012).

The condensation of 4-hydroxy-3,5-diphenyl-2-phenyliminothiazolidine **507a** with 5-fluoro-4-(4-methylpiperazino)- (**155t**) and 5-fluoro-4-morpholino- (**155u**) -1,2-DABs leads to regioisomeric thiazolo[3,4-*a*]quinoxalines **512** and **513** differing in substituents in positions 7 and 8 of the benzene ring (Scheme 2.119) (Mamedov et al. 2009b, 2012).

From the ratio of isomers formed it follows that the mesomeric effect of a fluorine atom in 1,2-DABs is comparable with the influence of an amino substituent.

The reactions of unsymmetric 4-hydroxythiazolidine **507d** with symmetrically substituted 1,2-DABs **155b**, **s** result in a mixture of 7,8-disubstituted thiazoloquinoxalines **509** and **514** (Mamedov et al. 2004a, 2009a), distinguished by substituents in the imine fragment, with the unsymmetrically substituted 1,2-DAB **155f** which proceed with the formation of the mixture of two pairs of regioisomeric thiazoloquinoxalinones with different substituents in positions 7 and 8 (**510a**, **511a** and **515a**, **516a**), distinguished by substituents in position 1 (Scheme 2.120) (Mamedov et al. 2009a).



Scheme 2.120 Reactions of unsymmetric 4-hydroxythiazolidines **507d** with the substituted 1,2-DABs **155b**, **f**, **n**, **s**

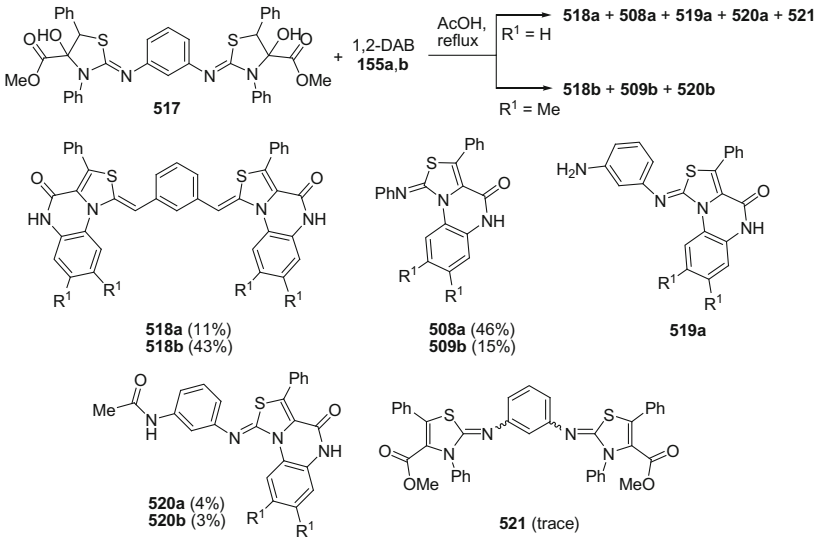
The condensation of 4-hydroxythiazolidine **507d** with 4-nitro-1,2-DAB **155n** (Scheme 2.120) affords a mixture of three out of four possible products (Mamedov et al. 2009a). This is indicated by the fact that the ^{1}H NMR spectrum of the crude product shows three doublets for the proton H(9) at δ10.69, 10.39, and 9.84 in the region diagnostic for thiazolo[3,4-*a*]quinoxalines. The ratio of products **510b**, **511b**, and **516b** in the crude mixture, calculated from the integral intensities of the diagnostic signals for the proton H(9) in the NMR ^{1}H spectrum, is 71:26:3.

The following should be kept in mind when carrying out the synthesis of bisthiazoloquinoxalines from bishydroxythiazolidine **517** according to the same scheme as in the synthesis of thiazoloquinoxalines **508** (Mamedov et al. 1999, 2004a, b) from monohydroxythiazolidine **507** (Schemes 2.117 and 2.119). All final products **518a**, **508a**, and **519a** predicted for the reaction of bishydroxythiazolidine **517** with 1,2-DAB **155a** were isolated (Scheme 2.121). The last product was obtained as the *N*-acetyl derivative **520a** upon the acylation of 1-(3-aminophenylimino)thiazolo[3,4-*a*]quinoxaline **519a** with acetic acid (solvent) (Scheme 2.121) (Mamedov et al. 2006).

Finally, apart from products **508a**, **518a**, **520a**, **519a**, 1,3-bisthiazoline **521** was obtained in low yield because of the dehydration of compound **517a**. In contrast the reaction of 1,2-DAB **155a** with compound **507a** afforded only thiazolo[3,4-*a*] quinoxaline **508a** (Mamedov and Levin 1996; Mamedov et al. 2004a, b).

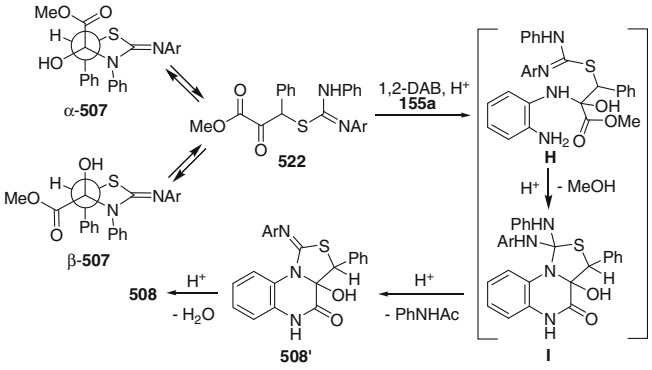
Reactions of **517** with the more basic 4,5-dimethyl-1,2-DAB **155b** generally proceed like reaction with 1,2-DAB **155a**. The exception was that bis(thiazolo [3,4-*a*]quinoxaline) **518b** was the major product, while thiazoloquinoxalines **509b** and **520b** were only by-products (Mamedov et al. 2006).

In spite of the fact that all of the 4-hydroxythiazolidines, considered here, in their crystalline phase exist in a cyclic form, in reactions with 1,2-DABs they react through the open-chain form **522** with the intermediate formation of a compound of



Scheme 2.121 Reaction of 1,3-bis(4′-hydroxy-4′-methoxycarbonyl-5′-phenylthiazolidine-2′-ylidenamino)benzene **517** with 1,2-DABs **155a**, **b**

type **H**. Probably, this progresses further by the bonding of the amino group of the aminal system to the amidine carbon atom. The thiazoloquinoxaline system **I**, with geminal aminophenyl and aminoaryl substituents at position 1, is then formed. Acid-catalyzed elimination of acetanilide from intermediate **I** leads to the covalent hydrate **508′** (Pozharskii 1985) which, under reaction conditions, loses water to produce the final products **508** in high yields (Scheme 2.122) (Mamedov et al. 2007).



Scheme 2.122 A plausible mechanism for the formation of thiazolo[3,4-*a*]quinoxalines

The following facts bear evidence to this mechanism:

(1) The existence of 4-hydroxythiazolidines in solution as a mixture of two diastereomers, which most probably convert into each other through an open-chain isothioureido structure.
(2) The formation of a mixture of thiazoloquinoxalines from the reaction of a separate nonsymmetrically substituted 4-hydroxythiazolidine with 1,2-DAB.
(3) The formation of 3a-hydroxy derivatives of thiazoloquinoxaline, *i.e.,* covalent hydrate **508′e**, and their complete conversion to final products—thiazoloquinoxaline **508e** in quantitative yields.

2.6.2.9 From 4-Hydroxyselenazolidines

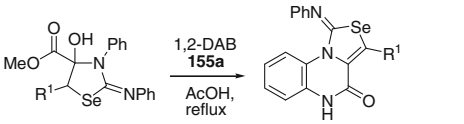
The condensation of 4-hydroxyselenazolidines **523a–c** with the non-substituted 1,2-DAB **155a** in boiling acetic acid results in the formation of the expected selenazolo[3,4-*a*]quinoxalines **524a–c**, the yields of which, in contrast to the yield (∼100 %) of the reaction with 4-hydroxythiazolidine **507a** with 1,2-DAB **155a** (Mamedov and Levin 1996; Mamedov et al. 2004a, b), do not exceed 6, 54, and 20 %, respectively (Scheme 2.123) (Mamedov et al. 2009c).

The reaction of 4-hydroxyselenazolidines **523b** with symmetrically substituted 1,2-DAB **155b** results in only one product–7,8-disubstituted selenazolo[3,4-*a*] quinoxalines **525**, with unsymmetrically substituted 1,2-DAB **155f**–a mixture of two isomeric selenazolo[3,4-*a*]quinoxalines **526** and **527**, differing by substituents in positions 7 and 8 with the domination of the first one. With unsymmetric 1,2-DAB **155n** the reaction proceeds with the formation of one of the two possible regioisomeric products, namely, the 8-substituted selenazoloquinoxaline **528** (Scheme 2.124) (Mamedov et al. 2009c).

2.6.2.10 From Alloxan

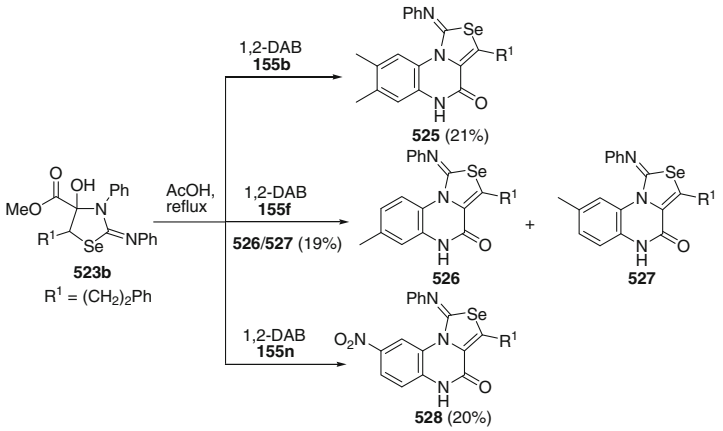
The reaction of alloxan **529** with 1,2-dimethylaminoaniline **530** in ethanol in the presence of hydrochloric acid, apart from other products, results in spiro-quinoxaline **531** in low yield (Scheme 2.125) (King and Clark-Lewis 1953).

Scheme 2.123 Synthesis of 1-phenylimino-3-substituted selenazolo[3,4-*a*]quinoxalin-4 (5*H*)-ones **524**

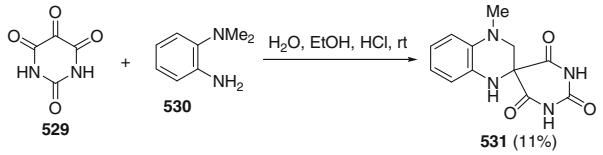


523 a R^1 = Ph
b R^1 = $(CH_2)_2$Ph
c R^1 = *n*-Hex

524 a R^1 = Ph (6%)
b R^1 = $(CH_2)_2$Ph (54%)
c R^1 = *n*-Hex (20%)



Scheme 2.124 Reactions of symmetric 4-hydroxyselenazolidine **523b** with the substituted 1,2-DABs **155b**, **f**, **n**



Scheme 2.125 The synthesis of 1,2,3,4-tetrahydro-4-methylquinoxaline-2-spiro-5′-(hexahydro-2′,4′,6′-trioxopyrimidine **531**

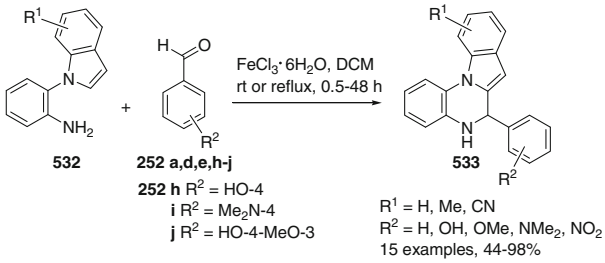
To our knowledge, this is the only case in which a 1,2-DAB derivative in the construction of the pyrazine ring of the quinoxaline system supplies five atoms (three carbon atoms and two nitrogen atoms), instead of four (two carbon and nitrogen).

2.6.2.11 From 2-(Indol-1-yl)aminobenzene

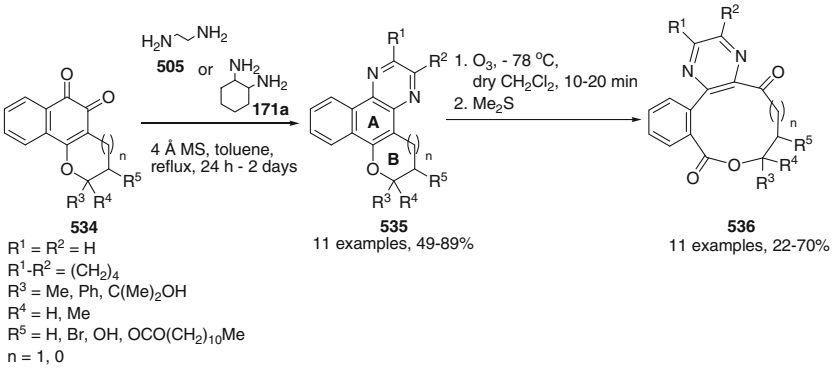
A series of new 5,6-dihydro-indolo[1,2-*a*]quinoxaline derivatives **533** has been prepared in moderate to excellent yields from 2-(indol-1-yl)benzenamines **532** with aromatic aldehydes **252a**, **d**, **e**, **h**–**j** by an efficient and economical iron-catalyzed Pictet–Spengler reaction (Scheme 2.126) (Xu and Fan 2011).

2.6.2.12 From Pyran-naptoquinones

When benzo[*a*]furo(pyrano)[2,3-*c*]phenazine derivatives **535** obtained by condensation of the 1,2-quinones **534** with 1,2-ethylendiamine **505** or *trans*-1,2-DACH



Scheme 2.126 Synthesis of 5,6-dihydro-indolo[1,2-*a*]quinoxalines **533** via Pictet–Spengler reaction promoted by $FeCl_3 \cdot 6H_2O$



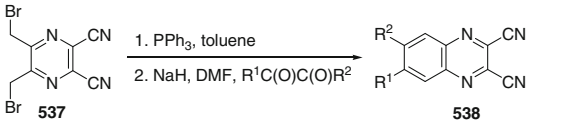
Scheme 2.127 Synthesis of 9- and 10-membered macrolactones **536**

171a (Woo et al. 2002) were treated with ozone, a selective oxidative cleavage of the enol double bond shared by rings **A** and **B** takes place with the formation of corresponding macrolactones **536** (Scheme 2.127) (Pérez-Sacau et al. 2005).

The enol double bond shows a behavior similar to the 9,10 double bond in polyaromatic phenanthrene systems, which is the most labile in terms of its chemical reactivity, and is readily broken under oxidative conditions to yield dialdehydes or acid derivatives (Burton et al. 2000; Huang et al. 2003).

The non-prenyl 1,2-naphthoquinones **534** were obtained correspondingly through the Knoevenagel condensation of lawsone (2-hydroxy-1,4-naphthoquinone) with paraformaldehyde $(CH_2O)_n$ leading to a quinone methide intermediate, which undergoes a HDAR with styrene as dienophile (Nair and Treesa 2001). Treatment of lawsone with CAN and styrene (Kobayashi et al. 1996; Sun et al. 1998) also yielded the dihydrofuran-naphthoquinone derivatives via [3 + 2]-type cycloaddition in a one-pot reaction (Pérez-Sacau et al. 2005).

Scheme 2.128 Synthesis of 2,3-dicyanoquinoxalines **538**



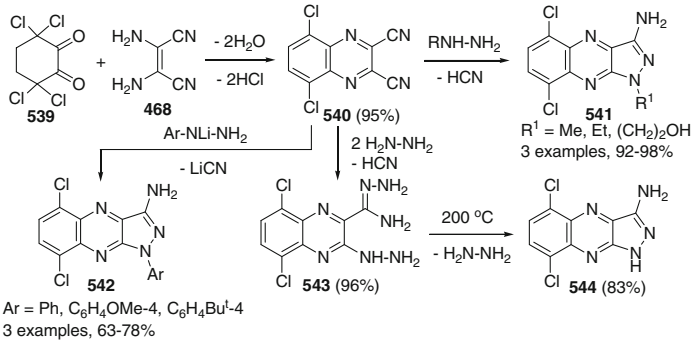
2.6.3 *Synthesis of Quinoxalines from Heterocyclic Systems with a Pyrazine Ring*

In quinoxaline synthesis, α-diketones can participate in the formation of a benzene rather than a pyrazine ring. Thus, 2,3-dicyanoquinoxalines **538** were prepared by the Wittig reaction of 2,3-bis(bromomethyl)-5,6-dicyanopyrazine **537** with α-dicarbonyl compounds (Scheme 2.128) (Jaung et al. 1998).

2.7 Synthesis of Quinoxalines Based on the Carbocyclic System

2.7.1 *From 3,3,6,6-Tetrachloro-1,2-cyclohexanedione*

Given that tetrachlorocyclohexanedione **539** (Guirado et al. 1997) can be used as a synthetic equivalent of unavailable 3,6-dichloro-1,2-benzoquinone, it was reacted with diaminomaleonitrile **468** to provide successfully, 5,8-dichloro-2,3-dicyanoquinoxaline **540** in quantitative yield (Scheme 2.129) (Guirado et al. 2011). On exploring the reactions between nucleophilic reagents and the latter, a



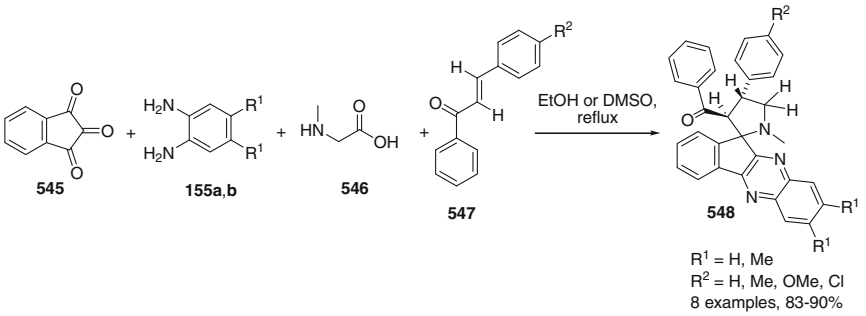
Scheme 2.129 Synthesis and reactions of 5,8-dichloro-2,3-dicyanoquinoxaline **540** with amines and hydrazines

crucially different chemical behavior in this compound from that of its non-chlorinated analogs, 2,3-dicyanoquinoxaline, was found. For example, 2,3-dicyanoquinoxaline reacts with ammonia (Rothkopf et al. 1975) or hydrazine (Ahmad et al. 1996; Brown 2006) undergoing nucleophilic addition to cyano groups, whereas with quinoxaline **540**, products involving the nucleophilic aromatic substitution of a cyano group result. It seems clear that the differing behavior between these compounds is caused by the conjunction of the electron-withdrawing groups present in quinoxaline **540**. Related reactions in quinoxaline derivatives have been described for 2,3-dichloroquinoxaline (Gobec and Urleb 2004; Brown 2006) and 3-chloro-2-cyanoquinoxaline (Monge et al. 1988, 1993), in which the nucleophilic displacement of the chlorine atom, but not of the cyano group, takes place.

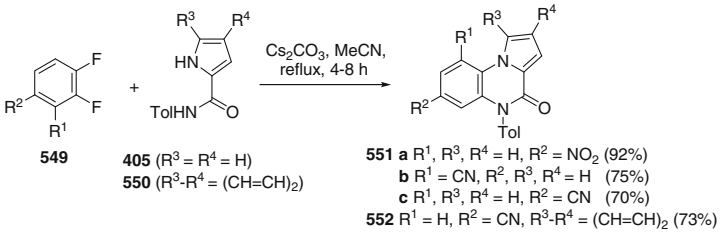
It should be pointed out that this is the only effective method for the synthesis of amino quinoxalines that can compete with any method based on the three-component condensation of 1,2-DAB, an aldehyde or ketone, and an isocyanide in the presence of a catalytic amount of *p*-TsOH, proposed and developed by Shaabani (2008) (see Sect. 2.2.11).

2.7.2 From Ninhydrin

New spiro[indeno[1,2-*b*]quinoxaline-11,2′-pyrrolidine] derivatives **548** were prepared stereoselectively in high yields from the efficient multicomponent 1,3-dipolar cycloaddition reaction between ninhydrin **545**, 1,2-DABs **155a**, **b**, sarcosine **546**, and chalcones **547** (Scheme 2.130) (Moemeni et al. 2012). In this case the carbocyclic system of the ninhydrin contributes to the construction of the pyrazine ring system, as distinct from the above reaction of tetrachlorocyclohexanedione **539**.



Scheme 2.130 Synthesis of spiro[indeno[1,2-*b*]quinoxaline-11,2′-pyrrolidine] **548**



Scheme 2.131 Synthesis of pyrrolo[1,2-*a*]- and indolo[1,2-*a*]quinoxalines

2.7.3 From 1,2-Difluorobenzene

Pyrrolo[1,2-*a*]- (**551a–c**) and indolo[1,2-*a*]- (**552**) quinoxalines were synthesized in good to excellent yields when pyrrole-2-carboxamide **405** and indole-2-carboxamide **550** were used in the presence of Cs_2CO_3 in reactions with 1,2-difluorobenzenes **549** under reflux in MeCN (Scheme 2.131) (Huang et al. 2011).

2.8 Conclusion

This survey has highlighted the application of a broad range of modern synthetic methods for the preparation of derivatives of quinoxaline as an important class of benzoheterocycle. Undoubtedly, among the methods for synthesizing quinoxaline derivatives, the most widely used are those based on the condensation of 1,2-DABs with α-dicarbonyl compounds (Hinsberg–Körner reaction), mostly α-diketones, or their equivalents.

As can be seen from the data presented in this chapter, there have recently appeared many original and interesting methods for the synthesis of quinoxalines, which are difficult to obtain or in general are unobtainable using the Hinsberg–Körner reaction. These new methods are based on the reactions of a wide variety of compounds that deserve further mention.

The Kaufmann method–pyrazinoannulation–uses aniline or its ring-substituted derivatives with 1,1,2-trichloro-2-nitroethene, with the formation of quinoxaline-2(1*H*)-on-4-oxide derivatives.

The Tanimori method involves reactions of 2-haloanilines with a variety of α-amino acids leading to the formation of quinoxaline-2(1*H*)-ones.

The Kalinski method uses the Ugi(4CR) reaction of 2-bromoanilines, ketones/aldehydes, a carboxylic acid and an isocyanide in polar protic solvents, and the Pd-catalyzed intramolecular N-arylamidation with the formation of N^1-alkyl and N^4-acyl derivatives of quinoxalin-2-ones.

The Shaabani method is a three-component condensation reaction of 1,2-DABs with diverse carbonyl compounds and isocyanides in the presence of a catalytic *p*-TsOH with the formation of highly substituted 3,4-dihydroquinoxalin-2-amines involving spiro-cyclic compounds.

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Chapter 3
Synthesis of Pyrrolo[l,2-*a*]quinoxalines

3.1 Pyrrolo[1,2-*a*]quinoxalines Based on Quinoxalines

3.1.1 Introduction

Derivatives of pyrrolo[1,2-*a*]quinoxalines (Fig. 3.1) have valuable characteristics and, in particular, marked biological activity and are a subject of constant interest. In spite of this, however, data on the synthesis of these compounds remain disconnected. The only review (Cheeseman and Cookson 1979), devoted to pyrroloquinoxalines and appearing in a monograph published in 1979, presents data mostly covering the period from 1965 to 1975. The chapter is devoted not only to the synthesis of pyrrolo[1,2-*a*]quinoxalines but also to the synthesis of pyrrolo[2,3-*b*]-, pyrrolo[3,4-*b*]-, and pyrrolo[1,2,3-*de*]quinoxalines and their physicochemical characteristics. While covering so many questions in a single review, the authors simply present the existing information without analyzing the methods used for their synthesis. From the chapter it is difficult to form an opinion as to which of the methods is more promising and to think of any new methods for their synthesis.

In the present chapter, an attempt is made to examine all possible ways of assembling the pyrrolo[1,2-*a*]quinoxaline skeleton from various fragments on the basis of an analysis of its structure.

*3.1.2 Possible Variants of the Construction of the Pyrrolo [1,2-*a*]quinoxaline System on the Basis of Quinoxalines*

Without touching on the integrity of the benzene ring, the creation of the pyrrolo [1,2-*a*]pyrazine system can be represented by one of the five types of construction depending on the number of atoms entering into the composition of the initial

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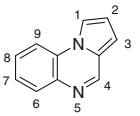


Fig. 3.1 The structure of pyrrolo[1,2-*a*]quinoxaline

fragments (Fig. 3.2): **QA** (9 + 0), **QB** (8 + 1), **QC** (7 + 2), **QD** (6 + 3), **QE** (6 + 2 + 1 or 6 + 1 + 2); the number of atoms in each of the fragments is given in parentheses. In other words, the synthetic equivalents that correspond to the principles of construction of heterocycles of type **QA** must consist of a fragment capable of undergoing intramolecular cyclocondensation. Each of the next three types (**QB**–**QD**) of construction of the tricyclic system requires two reagents corresponding to two synthetic equivalents: in the case of **QB** one- and eight-atom; in the case of **QC** two- and seven-atom; in the case of **QD** three- and six-atom. Case **QE** requires three reagents corresponding to three synthetic equivalents: six-, two-, and one-atom or six-, one-, and two-atom. Such an approach will make it possible to correlate the theoretically possible schemes of assembly to real syntheses, while taking account of the nature of the reaction centers. This makes it possible not only to rationalize already known methods of synthesis but also to determine which of the methods of assembly have not yet been used and why and to attempt to "think up" new reactions by means of which the pyrrolo[1,2-*a*]quinoxaline system could be constructed.

All known methods for the synthesis of the pyrrolo[1,2-*a*]quinoxaline system can be divided into three groups. The first group of methods is based on derivatives of quinoxaline, the second group contains methods based on pyrroles, and the third group contains other methods including the recyclization of other heterocycles and also syntheses from nonheterocyclic systems. This chapter examines methods of synthesis based on derivatives of quinoxaline and the methods of the third group. Possible variants of the construction of the pyrrolo[1,2-*a*]quinoxaline system based on quinoxalines are presented below.

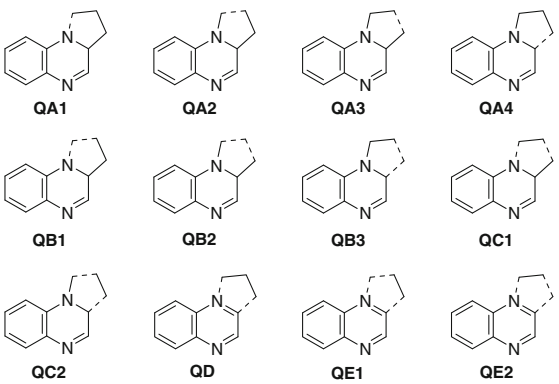


Fig. 3.2 Possible variants of the construction of the pyrrolo [1,2-*a*]quinoxaline system on the basis of quinoxalines

3.1.3 Production Methods of Type QA (Version QA1)

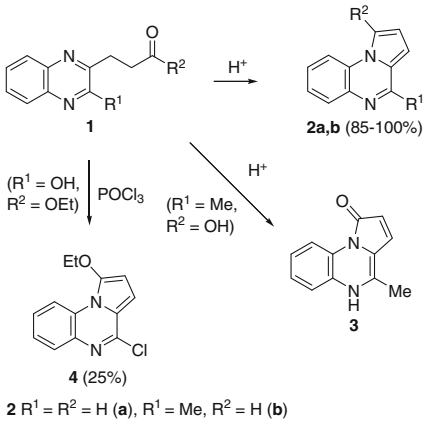
One of the most widespread and most widely used among methods for the synthesis of pyrrolo[1,2-*a*]quinoxalines is the method involving the intramolecular cyclization of derivatives of quinoxaline with substituents at position 2 and containing at least three carbon atoms with reaction centers capable of nucleophilic attack. Quinoxalines **1**, containing a γ-carbonylalkyl substituent at position 2 (ketones, carboxylic acids, esters) undergo intramolecular cyclization under the influence of acids with the formation of pyrroloquinoxalines **2–4** (Scheme 3.1) (Kumashiro 1961; Taylor and Hand 1962, 1963; Cheeseman and Roy 1969).

Reduction of the quinoxalines **5** leads to hydropyrroloquinoxalines **6–8** (Nelson and Boyer 1950; Okumura and Shigemitsu 1965). The pyrrolo[1,2-*a*]quinoxaline system (compound **6**) was first obtained by this method (Okumura and Shigemitsu 1965). During the reductive cyclization of ethyl quinoxalin-2-yl- and 3-methylquinoxalin-2-ylpyruvates **5** in the presence of copper chromite at high temperature, the perhydropyrrolo[1,2-*a*]quinoxalines **7** and **8** are formed (Scheme 3.2).

During closure of the pyrrole ring as a result of the treatment of compound **9** with PBr_3, a mixture of dibromo- and tribromopyrroloquinoxalines **10** and **11** is formed (Scheme 3.3) (Cheeseman and Roy 1968).

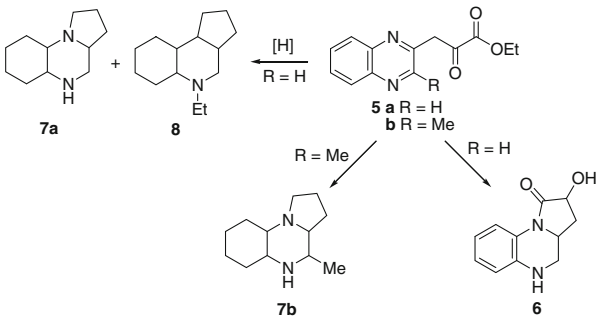
During the action of HBr, 2,3-dihydroxypropyl-4-methylquinoxaline **12** undergoes intramolecular cyclization with the formation of 4-methylpyrrolo[1,2-*a*]quinoxaline **13** (Scheme 3.4) (Cheeseman and Tuck 1965a).

When treated with concentrated hydrochloric acid in methanol, the 2-(2-ylidene)acetylquinoxalines **14**, easily obtained from the corresponding 2-acetylquinoxalines and aryl(hetaryl)aldehydes, form 1-substituted derivatives of pyrrolo[1,2-*a*]quinoxalines **15a–i**. Intramolecular closure also occurs successfully in solution in CCl_4 in the presence of molecular bromine, but here the dibromide **16** is formed (Matoba et al. 1980, 1981). The use of compounds **14** (R^1 = Me, R^2 = CH=CHAr)



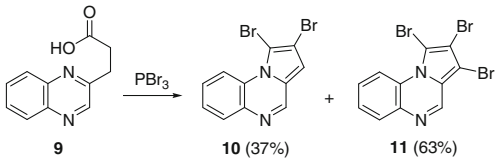
2 $R^1 = R^2 = H$ (**a**), R^1 = Me, $R^2 = H$ (**b**)

Scheme 3.1 Intramolecular cyclization of quinoxalines containing a γ-carbonylalkyl substituent

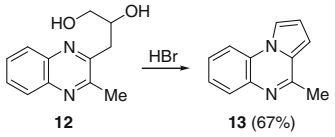


Scheme 3.2 Intramolecular cyclization of quinoxalines containing an ethyl 2-oxopropanoate aragment

Scheme 3.3 Intramolecular cyclization of 3-(quinoxalin-2-yl)propanoic acid



Scheme 3.4 Intramolecular cyclization of 3-(3-methylquinoxalin-2-yl) propane-1,2-diol

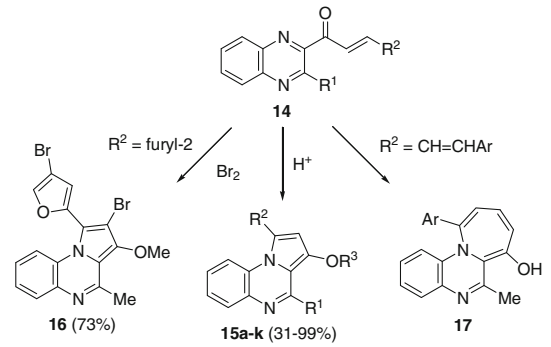


(Matoba et al. 1983), which have competing reaction centers capable of undergoing nucleophilic attack, in this reaction leads not to the supposed derivatives of azepino [1,2-*a*]quinoxaline **17** but to the formation of the pyrrolo[1,2-*a*]quinoxalines **15j**, **k** (Scheme 3.5).

When ethanol solutions of 2-cinnamoyl-3-methylquinoxaline 4-oxide **18a** and 3-methyl-4-oxido-2-quinoxalinyl 5-phenylpenta-2,4-dienyl ketone **18b** are boiled in the presence of hydrochloric acid, the respective 4-methyl-3-oxo-1-phenyl- and 4-methyl-3-oxo-1-(2-phenylethenyl)-3*H*-pyrrolo[1,2-*a*]quinoxalin-10-ium chlorides **19a**, **b** are formed similarly with quantitative yields (Scheme 3.6) (Matoba et al. 1987).

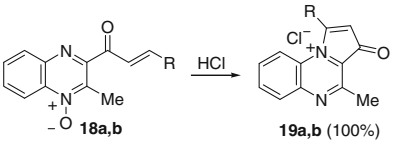
The double bond of the ethenoyl function can enter the aromatic system. Thus, substituted derivatives of benzoylquinoxaline **20** undergo cyclization during UV irradiation; the cyclization is accelerated by the presence of trifluoroacetic or *p*-toluenesulfonic acid (Scheme 3.7) (Atfah et al. 1990).

The proposed mechanism of photocyclization for the transformation **20b → 21b** and the role of protonation are clear from the scheme (Scheme 3.8) (Atfah et al. 1990).



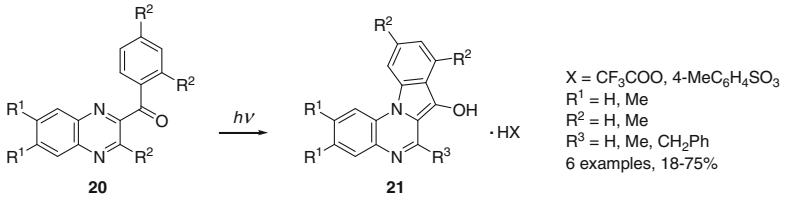
15 R^1 = H, R^2 = furyl-2 (**a,b**): R^3 = H (**a**), Me (**b**);
R^1 = Me (**c-k**):
R^2 = furyl-2, R^3 = H (**c**), R^2 = furyl-2, R^3 = Me (**d**), R^2 = Ph, R^3 = Me (**e**),
R^2 = Ph, R^3 = Ac (**f**), R^2 = C_6H_4OMe-4, R^3 = Me (**g**), R^2 = $C_6H_4NO_2$-4, R^3 = H (**h**),
R^2 = $C_6H_4NO_2$-4, R^3 = $COC_6H_3NO_2$-4 (**i**), R^2 = CH=CHPh, R^3 = H (**j**),
R^2 = $CH=CHC_6H_3NO_2$-4, R^3 = H (**k**)

Scheme 3.5 Intramolecular cyclization of quinoxalines with 2-en-1-one moiety at position 2

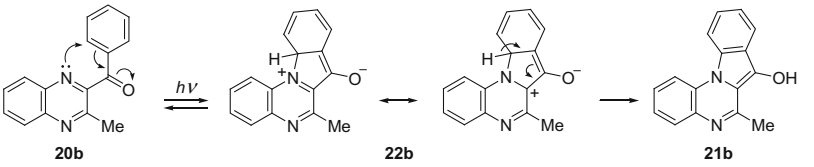


18, 19 R = Ph (**a**), CH=CHPh (**b**)

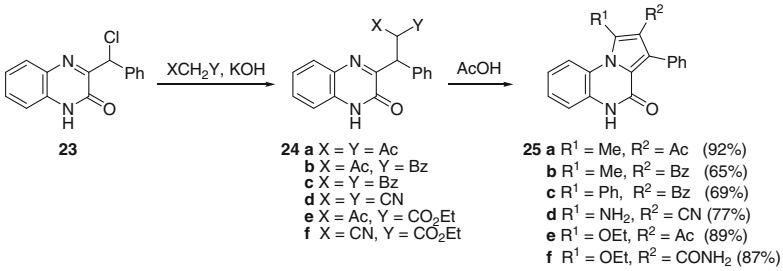
Scheme 3.6 Intramolecular cyclization of quinoxaline-4-oxides with 2-en-1-one moiety at position 2



Scheme 3.7 Cyclization of aroylquinoxalines when exposed to UV irradiation



Scheme 3.8 Proposal mechanism of photocyclization



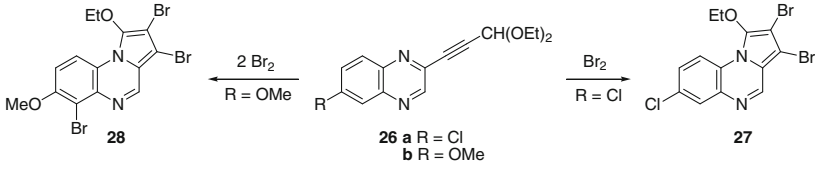
Scheme 3.9 Acid-catalized cyclization of the quinoxalines with β-dicarbonyl, β-dinitrile, and β-nitrilecarbonyl moieties

The quinoxalines **24** with β-dicarbonyl, β-dinitrile, and β-nitrilecarbonyl fragments, produced in the reaction of 3-(α-chlorobenzyl)quinoxalin-2-one **23** with the anions of β-dicarbonyl compounds, dicyanomethane, and cyanoacetic ester, form the pyrroloquinoxalines **25** when treated with acetic acid (Scheme 3.9) (Mamedov et al. 2004). This cyclization could lead to one and/or two compounds differing in the position of the substituents R^1 and R^2, but only the tricyclic compounds **25a–f** are formed as a result of the reaction.

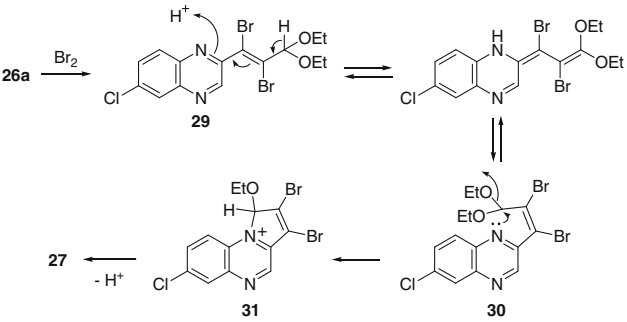
6-Chloro-2-(3,3-diethoxypropyn-1-yl)quinoxaline **26a**, obtained by the cross-coupling of 2,6-dichloroquinoxaline and 3,3-diethoxypropyne, forms the pyrroloquinoxaline **27** when treated with molecular bromine. If the 6-methoxy derivative of quinoxaline **26b** is used in this reaction, position 5 of the initial quinoxaline ring undergoes bromination on account of the strong electron-donating effect of the methoxyl group, and this leads to the tribromo derivative of pyrrolo [1,2-*a*]quinoxaline **28** (Scheme 3.10).

The pyrroloquinoxaline **27** is formed through a stage involving initial *trans* addition of bromine at the triple bond (the formation of compound **29**) followed by prototropic isomerization to the *cis* isomer **30**, which undergoes cyclization to the pyrroloquinoxaline with the elimination of alcohol (Scheme 3.11) (Armengol and Joul 2001).

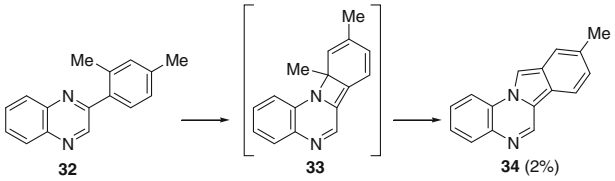
An essential condition for the closure of the pyrrole ring according to type **QA** in 2-substituted quinoxalines is the presence of a three-carbon fragment, and it is not necessary here that the γ-carbon atom of this fragment initially contained a suitable reaction center. In certain cases, the reaction centers can arise under the reaction



Scheme 3.10 Cyclization of 2-(3,3-diethoxypropyn-1-yl)quinoxalines when exposed to bromine



Scheme 3.11 Proposal mechanism of cyclization when exposed to bromine

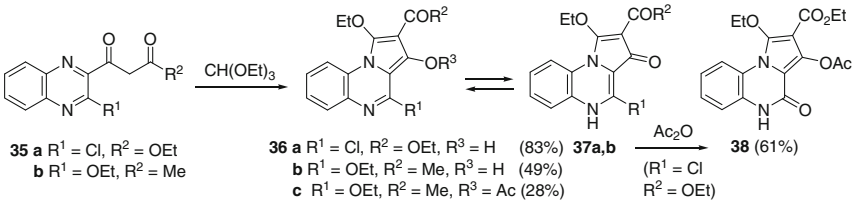


Scheme 3.12 Pyrolysis of 2-(2,4-dimethylphenyl)quinoxaline

conditions. For example, the pyrolysis of 2-(2,4-dimethylphenyl)quinoxaline **32** at 550–560 °C in the presence of the industrial dehydrogenation catalyst K-16 (Prostakov 1976) leads to 9-methylisoindolo[2,1-*a*]quinoxaline **34** (Scheme 3.12) (Pleshakov et al. 1983).

3.1.4 Production Methods of Type QB (Version QB1)

During the condensation of ethyl (3-chloro-2-quinoxaloyl)acetate **35a** with orthoformic ester in the presence of Ac_2O (65–70 °C), the formation of two substances was observed: the main chlorine-containing reaction product **36a** and a minor chlorine-free compound **38** (Scheme 3.13). The amount of compound **38** increased with increase in temperature, and at 100–105 °C it became the main reaction product. It was also shown that compound **36a** can be obtained by heating the initial compound **35a** with orthoformic ester at a higher temperature (100–105 °C). The chain **35a** → **36a** → **38** was therefore investigated (Eiden and Bachmann 1973; Glushkov et al. 1988). The condensation of the quinoxaline **35b** with orthoformic ester at a higher temperature (up to 160 °C) leads to the pyrroloquinoxalines **36b and 36c**.



Scheme 3.13 Condensation of ethyl (3-chloro-2-quinoxaloyl)acetate and 1-(3-ethoxyquinoxalin-2-yl)butane-1,3-dione with orthoformic ester in the presence of Ac_2O

3.1.5 Production Methods of Type QB (Version QB3)

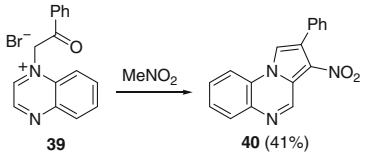
The reaction of 1-phenacylquinoxalinium bromide **39** with nitromethane in its boiling solution in the presence of Na_2CO_3 for 6 h leads to 3-nitro-2-phenylpyrrolo [1,2-*a*]quinoxaline **40** (Scheme 3.14) (Kiel and Krohnke 1972).

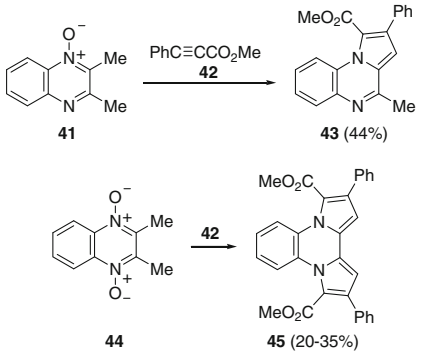
3.1.6 Production Methods of Type QC (Version QC1) Cycloaddition Reactions

As a rule, in these reactions, the quinoxaline derivative directly or indirectly fulfills the function of a 1,3-dipolar compound, and this determines the path to the formation of the final product–pyrrolo[1,2-*a*]quinoxaline–and its structure almost irrespective of the nature of the 1,3-dipolarophile. During the reaction of 2,3-dimethylquinoxaline monooxide **41** and 2,3-dimethylquinoxaline dioxide **44** with methyl phenylpropargylate **42** in molar ratios of 1:1 and 1:2, respectively, compounds **43** and **45** are formed (Scheme 3.15) (Kaupp et al. 1987).

It is well known that maleic anhydride **46a** is capable of undergoing three types of reaction: condensation with dienes with the participation of the double bond and the formation of a Diels–Alder adduct; addition at the double bond with the formation of a derivative of succinic anhydride; reaction of one of the carbonyl groups followed by opening of the anhydride system (Schönberg and Mustafa 1943; Flett and Gardner 1952). Compounds **47**–**50** could be formed in the reaction of maleic anhydride with 2,3-dimethylquinoxaline **51a** (Fig. 3.3).

Scheme 3.14 Cyclization of 1-phenacylquinoxalinium bromide when exposed to nitromethane





Scheme 3.15 Reactions of 2,3-dimethylquinoxaline mono- and dioxides with methyl phenylpropargylate in various molar ratios

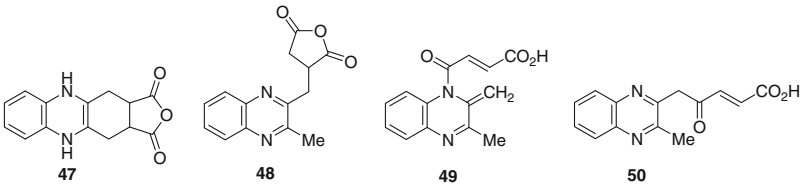
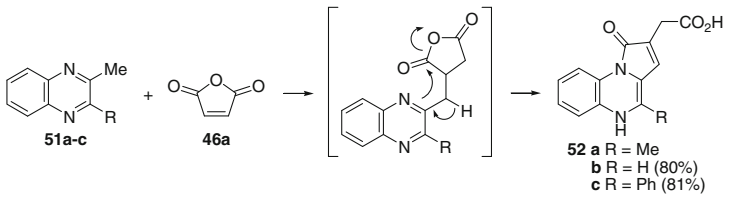


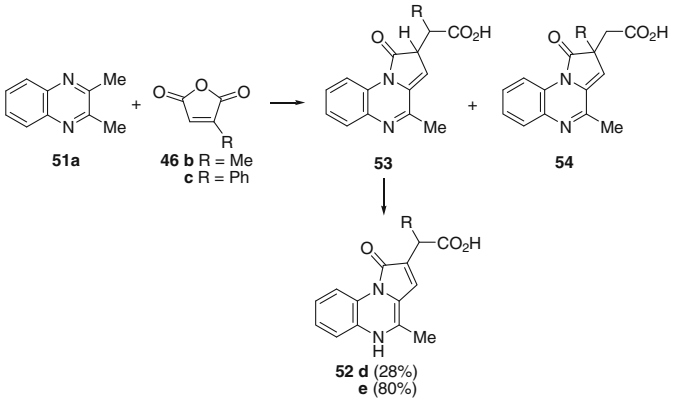
Fig. 3.3 The reaction products of 2,3-dimethylquinoxaline with maleic anhydride

However, the reaction of 2,3-dimethylquinoxaline **51a** with maleic anhydride **46a** under standard conditions (Taylor and Hand 1963) takes place with the formation of a compound with the empirical formula $C_{14}H_{12}N_2O_3$, the IR spectrum of which does not contain bands for the stretching vibrations of the anhydride groups but there are bands for the stretching vibrations characteristic of NH, the OH of the carboxyl function, the double bond, and an amide vinylog (Scheme 3.16). The NMR spectra and the chemical properties of the "adduct" show that pyrrolo[1,2-*a*]quinoxaline **52a** is formed as a result of the reaction, and this can be represented by the Scheme 3.16 (Taylor and Hand 1962, 1963). Accordingly, the condensation of maleic anhydride with 2-methylquinoxaline and 2-methyl-3-phenylquinoxaline gives 2-carboxymethyl- **52b** and 2-carboxymethyl-4-phenylpyrrolo[1,2-*a*]quinoxalin-1(5*H*)-ones **52c** (Taylor and Hand 1963; Taylor and Cheeseman 1964).

In the case of monosubstituted derivatives of maleic anhydride, the two possible isomeric succinic anhydrides are formed; as a result of opening and closure of the ring, like the unsubstituted derivatives, they give 1-oxo-1,2-dihydropyrrolo[1,2-*a*]quinoxalines **53** and **54**, and here only the first of them isomerize to the 1-oxo-1,5-dihydropyrrolo[1,2-*a*]quinoxalines **52d**, **e** (Scheme 3.17) (Cheeseman and Tuck 1965a).



Scheme 3.16 Reactions of 2,3-dimethylquinoxalines with maleic anhydride



Scheme 3.17 Reactions of 2,3-dimethylquinoxaline with maleic anhydride derivatives

If disubstituted maleic anhydride is used in this reaction, even with boiling in toluene solution for 46 h, the process does not go past the stage of formation of the corresponding derivative of succinic acid–3-[(3-methylquinoxalin-2-yl)methyl]-3,4-diphenyldihydrofuran-2,5-dione **55** (Fig. 3.4), which is isolated with a yield of 90 % (Cheeseman and Tuck 1965a).

The authors of (Taylor and Hand 1962) cast some doubt on all the previous investigations (Flett and Gardner 1952; Schönberg and Mustafa 1943) concerning study of the reaction of 2,3-dimethylquinoxaline with maleic anhydride, the products of which were erroneously assigned one of the above-mentioned structures **47**–**50** (Fig. 3.3), and showed that pyrrolo[1,2-*a*]quinoxaline is formed as a result of this reaction.

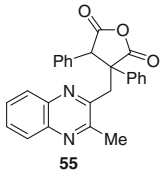
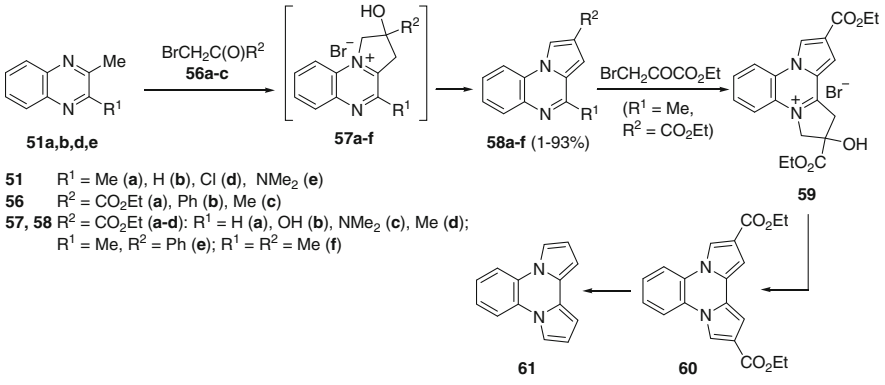


Fig. 3.4 The structure of 3-[(3-methylquinoxalin-2-yl)methyl]-3,4-diphenyldihydrofuran-2,5-dione

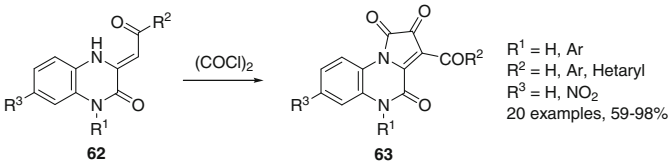
The second general method for the synthesis of pyrrolo[1,2-*a*]quinoxalines according to the **QC1** version involves the reaction of mono- and dimethylquinoxalines with α-halo ketones (Cheeseman and Tuck 1965a; Buchan et al. 1985; Berlin et al. 1991; Blache et al. 1995; Guillon et al. 1998, 2000). The tricyclic system in this case is produced after treatment of the intermediately formed quaternary salts **57a–f** with sodium alcoholate (Scheme 3.18). The effectiveness of the reaction depends on how successfully the quaternary salt is formed, and this in turn is determined by the nucleophilicity of the nitrogen atom of the quinoxaline system at which the reaction occurs and by the nature of the alkylating reagent. For example, the reaction of the ethyl bromopyruvate **56a** with 2,3-dimethylquinoxaline **51a** (Berlin et al. 1991) gives 93 % of the tricyclic compound **58d**, while the reaction of 2-chloro-3-methylquinoxaline **51d** (Blache et al. 1995) with ethyl bromopyruvate **56a** takes place with a yield of only 26 % of the pyrrolo[1,2-*a*] quinoxaline derivative **58b**. At the same time, only 14 % of the required substance **58e** is formed in the reaction of 2,3-dimethylquinoxaline **51a** with phenacyl bromide **56b** (Cheeseman and Tuck 1965a), and only 1 % of the pyrroloquinoxaline **58f** is formed with bromoacetone **56c**.

The presence of a methyl substituent at position 4 of compound **58d** made it possible, with identical strategy, to synthesize with a 56 % yield 2,11-di(ethoxycarbonyl)dipyrrolo[1,2-*a*;2′,1′-*c*]quinoxaline **60**, which was converted into unsubstituted dipyrrolo[1,2-*a*;2′,1′-*c*]quinoxaline **61** according to the scheme presented above (Berlin et al. 1991).

In a number of cases, the reaction of the quinoxalines **62** with oxalyl chloride with boiling in anhydrous chloroform at 60–63 °C for 2–2.5 h leads to the formation of 3-aroyl- and heteroyl-1,2,4,5-tetrahydropyrrolo[1,2-*a*]quinoxaline-1,2,4-triones **63** with sometimes almost quantitative yields (Scheme 3.19) (Andreichikov 1994; Tolmacheva et al. 2002; Maslivets et al. 2002; Bozdyreva et al. 2005).

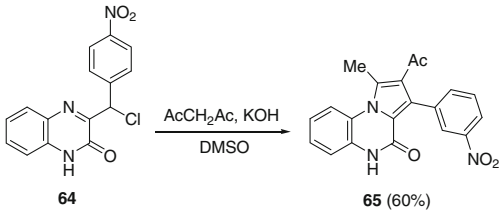


Scheme 3.18 Reactions of mono- and dimethylquinoxalines with α-halo ketones



Scheme 3.19 Reactions of the 3-(2-oxo-2-R^2-ethylidene)-3,4-dihydroquinoxalin-2(1*H*)-ones with oxalyl chloride

Scheme 3.20 Reaction of 3-[α-chloro(*p*-nitrobenzyl)] quinoxalin-2-one with acetylacetone



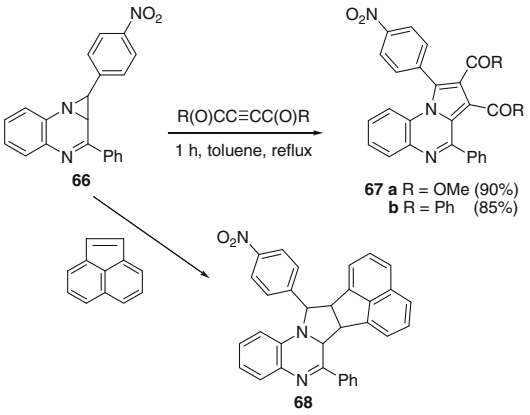
The reaction of 3-[α-chloro(*p*-nitrobenzyl)]quinoxalin-2-one **64** with acetylacetone in the presence of KOH without isolation of the corresponding *C*-alkylation product leads to the formation of the pyrroloquinoxaline **65** (Scheme 3.20) (Mamedov et al. 2004).

3.1.7 Production Methods of Type QC (Version QC2)

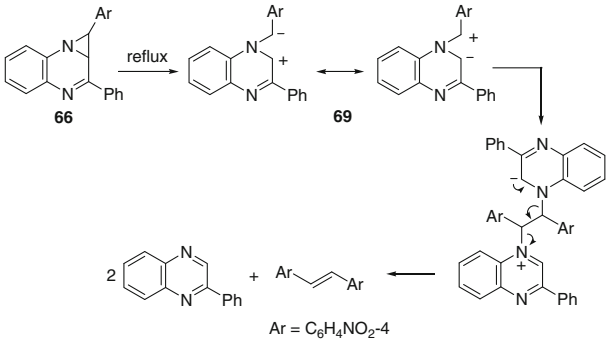
1-(*p*-Nitrophenyl)-2-phenyl-1,1*a*-dihydroazirino[1,2-*a*]quinoxaline **66**, readily obtainable by the reaction of 2,3-dibromo-3-(*p*-nitrophenyl)-1-phenyl-1-propanone with 1,2-diaminobenzene (1,2-DAB), reacts with 1,3-dipolarophiles—dimethyl acetylenedicarboxylate, dibenzoylacetylene, and acenaphthylene—in boiling toluene with the formation of derivatives of 1-*p*-nitrophenyl-4-phenylpyrrolo[1,2-*a*] quinoxaline **67** in the first two cases and 13-*p*-nitrophenyl-6-phenyl-6*a*,6*b*,12*b*, 13-tetrahydroacenaphtho[1′,2′:3,4]pyrrolo[1,2-*a*]quinoxaline **68** in the third (Heine and Henzel 1969) (Scheme 3.21).

The fact that these reactions take place through the 1,3-dipolar intermediate **69**, arising as a result of thermal cleavage of the C–C bond of the azirino[1,2-*a*] quinoxaline system, is favored by the formation of *p*,*p* -dinitrostilbene and 2-phenylquinoxaline (Heine and Henzel 1969) according to the following Scheme 3.22.

To realize the strategy for the synthesis of pyrrolo[1,2-*a*]quinoxalines denoted by the symbol **QC2** it could be possible to use the 1,3-dipolar cycloaddition of the quinoxalinium *N*-ylide, produced in situ by the reaction of 1-phenacylquinoxalium bromide with triethylamine, with various 1,3-dipolarophiles if the formation of the

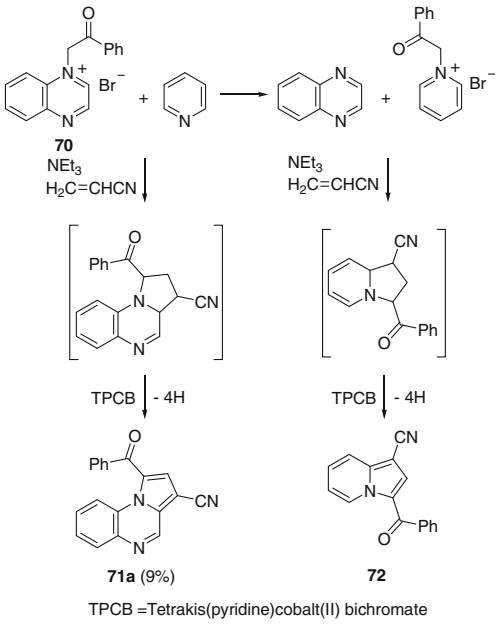


Scheme 3.21 Reactions of 1-(*p*-nitrophenyl)-2-phenyl-1,1*a*-dihydroazirino[1,2-*a*]quinoxaline with 1,3-dipolarophiles



Scheme 3.22 The thermal cleavage of azirino[1,2-*a*]quinoxaline derivatives

1-phenacylquinoxalinium bromide proceeded well and without side processes. Unfortunately, 1-phenacylquinoxalinium bromide is formed with a yield of only 28 % as a result of prolonged standing (one month) of the mixture of quinazoline and phenacyl bromide in chloroform solution (Easley and Bahner 1950). Boiling of the reaction mixture for 3 h leads to resin formation. When heated without a solvent for 10 min, the mixture of quinoxaline and phenacyl bromide polymerizes. Nevertheless, the desired salt can be obtained with a 30 % yield by fusion of the mixture of reagents at 60 °C for 5 min. Heating of a mixture of 1-phenacyl bromide, acrylonitrile, triethylamine, and Py–$Co(HCrO_4)_2$ in DMF solution at 80–90 °C for 5 h leads to the expected 1-benzoyl-3-cyanopyrrolo-[1,2-*a*]quinoxaline **71a** with a yield, unfortunately, of only 9 %. The main reaction product (59 %) is 3-benzoyl-1-cyanoindolizine **72** (Zhou et al. 1998, 1999). The 1,3-dipolar cyclic adduct **72** obviously results from reaction of the acrylonitrile with the



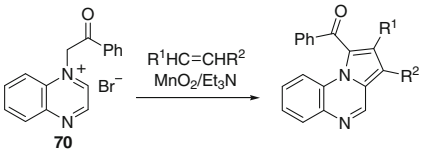
Scheme 3.23 Synthesis of 1-benzoyl-3-cyanopyrrolo[1,2-*a*]quinoxaline and 3-benzoyl-1-cyanoindolizine from 1-phenacylquinoxalium bromide and pyridine with the use of triethylamine and acrylonitrile

N-phenacylpyridinium bromide formed as a result of disproportionation of the salt **70** by pyridine (a stronger base than quinoxaline), which appears in the reaction mixture as a result of decomposition of the tetrakis(pyridine)cobalt(II) bichromate (Scheme 3.23).

In order to avoid this effect, an attempt was made to replace TPCB by the more readily accessible oxidizing agent MnO_2 (Scheme 3.24). Compound **71a** was formed with a yield of 48 %. When the analogous procedure was used, the pyrrolo[1,2-*a*]quinoxalines **71b–e** were obtained with moderate yields from methyl acrylate, methyl vinyl ketone, diethyl fumarate, and *N*-phenylmaleimide, respectively (Zhou et al. 1999).

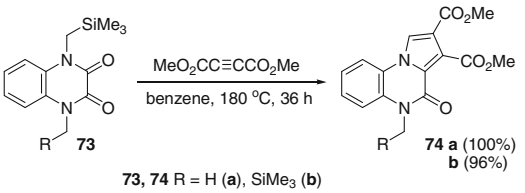
The quinoxalines **73** are converted by the action of acetylenedicarboxylic ester into the pyrroloquinoxalines **74** (Scheme 3.25) (Komatsu et al. 2003).

Another synthetic equivalent of the type **QC2** synthons in the construction of the pyrrolo[1,2-*a*]quinoxaline fragment entering in the condensed heterocyclic system



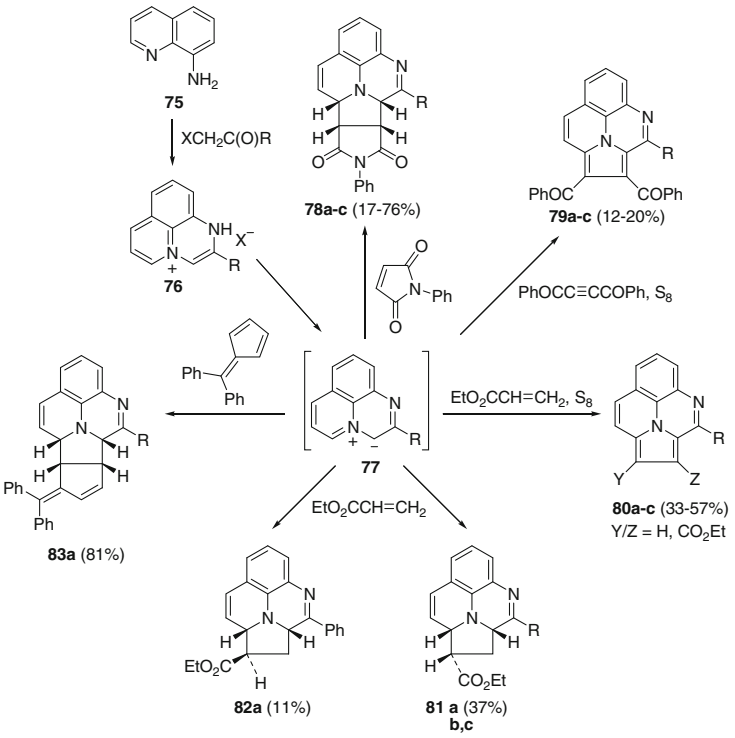
71 a R^1 = H, R^2 = CN (48%)
b R^1 = H, R^2 = CO_2Me (49%)
c R^1 = H, R^2 = COMe (52%)
d R^1 = R^2 = CO_2Et (48%)
e R^1-R^2 = C(O)NPhC(O) (40%)

Scheme 3.24 Synthesis of 1-benzoylpyrrolo[1,2-*a*]quinoxalines from 1-phenacylquinoxalinium bromide enes with the use of MnO_2 as oxidizing agent



Scheme 3.25 4-[(Ttrimethylsilyl)methyl]quinoxaline-2,3(1*H*,4*H*)-diones in the synthesis of pyrrolo[1,2-*a*]quinoxalines

can be the conjugated heterocyclic mesomeric betaines **77**, i.e., 2-substituted 1*H*-1,3*a*λ^5-diazaphenalen-3*a*-ium-3-ides produced in situ by the deprotonation of 2-substituted 1*H*-1,3*a*λ^5-diazaphenalen-3*a*-ium salts **76**, which are the products from condensation of 8-aminoquinoline **75** with α-halogeno ketones (Scheme 3.26) (Ollis and Stanforth 1989). Since the betaines **77** cannot be isolated on account of their high reactivity, they were characterized in the form of the adducts **78–83**, which are derivatives of the pyrroloquinoxalines produced as a result of 1,3-dipolar addition of the betaines **77** to the various acetylenic and olefinic dipolarophiles (Scheme 3.26).



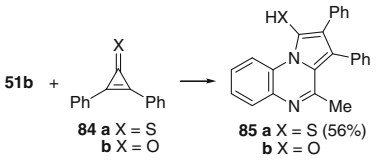
Scheme 3.26 Synthesis of condensed heterocyclic systems on the basis of 8-aminoquinoline

3.1.8 Production Methods of Type QD

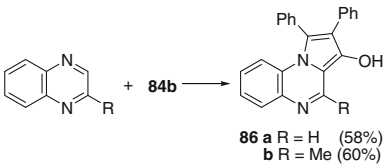
Diphenylcyclopropane and diphenylcyclopropanethione, being synthetic equivalents of synthon **QD**, react with various heterocyclic nitrogen compounds with annelation of the pyrrole ring; if the compound contains the –N=N– fragment, annelation as a rule involves both nitrogen atoms with the formation of a pyrazole-containing condensed system. In these reactions, 2-methylquinoxaline **51b** acts as a synthetic equivalent of synthon **QD** and, depending on the second reagent, is converted into the 1-hydroxy or 1-mercapto derivatives of pyrrolo[1,2-*a*] quinoxaline **85** (Scheme 3.27) (Lown and Matsumoto 1971a, b).

However, a more recent investigation, involving study of the reaction of diphenylcyclopropenone **84b** with quinoxaline and 2-methylquinoxaline, showed that the 3-hydroxy derivative of pyrrolo[1,2-*a*]quinoxaline **86** (Weidner et al. 1991) and not the 1-hydroxy derivative **85b**, as reported previously (Lown and Matsumoto 1971a), is formed as a result of this reaction (Scheme 3.28).

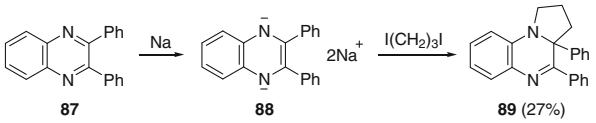
1,3-Diiodopropane can act as a more accessible synthetic equivalent of the three-carbon synthon in the construction of the pyrrolo[1,2-*a*]quinoxaline system by strategy **QD**. By reaction with 1,3-diiodopropane in solution for 1 h, the dianion of 2,3-diphenylquinoxaline **88**, produced by the reaction of 2,3-diphenylquinoxaline **87** with two equivalents of metallic sodium, gives 3α,4-diphenyl-1,2,3,3α-tetrahydropyrrolo[1,2-*a*]quinoxaline **89** (Scheme 3.29) (Smith and Levi 1972).



Scheme 3.27 Reactions of diphenylcyclopropane and diphenylcyclopropanethione with the 2-methylquinoxaline



Scheme 3.28 Diphenylcyclopropane as synthetic equivalent of synthon QD in the pyrrolo[1,2-*a*] quinoxaline synthesis



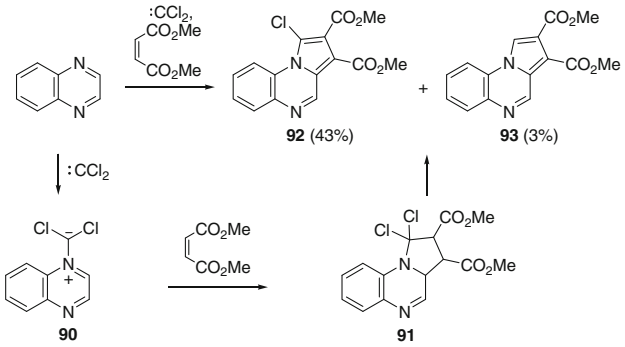
Scheme 3.29 Reaction of 1,3-diiodopropane with the dianion of 2,3-diphenylquinoxaline

3.1.9 Production Methods of Type QE1

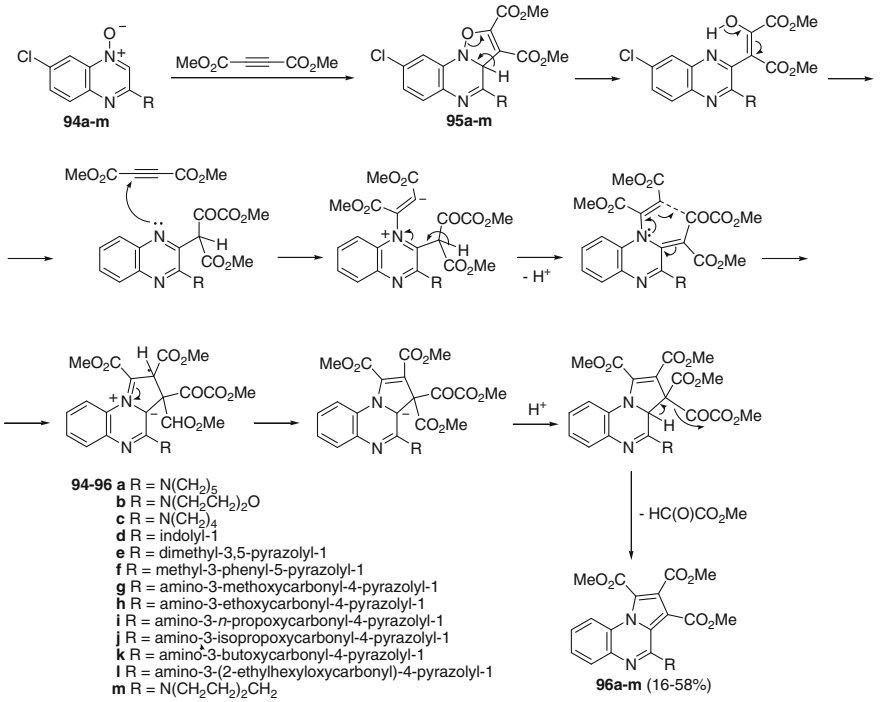
A more thorough retrosynthetic analysis of the structure of pyrrolo[1,2-*a*]quinoxalines demonstrates the possibility of synthesizing these compounds by a three-component reaction using reagents that can supply the one- and two-carbon fragments and also the quinoxaline system (symbol **QE1**). The reaction of dichlorocarbene, generated from chloroform by the action of KOH, with quinoxaline in the presence of dimethyl maleate goes through the intermediate formation of an ylide–cycloammoniodichloromethanide **90**, the 1,3-dipolar cycloaddition of which to dipolarophiles gives the unstable derivatives of tetrahydropyrrolo[1,2-*a*]quinoxalines **91**; they are dehydrogenated under the reaction conditions or by the action of an oxidizing agent to derivatives of pyrrolo[1,2-*a*]quinoxalines. In this case, pyrrolo[1,2-*a*]quinoxaline **92** and trace quantities of its analog **93** not containing chlorine are formed (Scheme 3.30) (Khlebnikov et al. 1998).

3.1.10 Production Methods of Type QE2

As a result of 1,3-dipolar addition to dimethyl acetylenedicarboxylate and methyl propargylate and depending on the molar ratio of the latter, the quinoxaline *N*-oxides **94a–m** are transformed selectively into derivatives of isoxazolo[2,3-*a*]quinoxaline **95a–m** and pyrrolo[1,2-*a*]quinoxaline **96a–m** (Scheme 3.31) (Kim et al. 1989, 1990a, b, c, 2000, 2001).



Scheme 3.30 A three-component reaction in the pyrrolo[1,2-*a*]quinoxaline derivatives synthesis



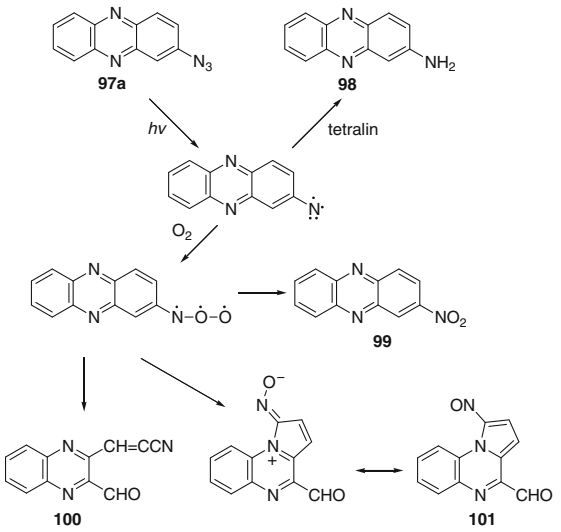
Scheme 3.31 1,3-Dipolar addition of the quinoxaline *N*-oxides to dimethyl acetylenedicarboxylate

3.1.11 Other Methods of Synthesis

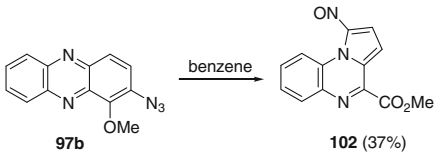
Under these methods of synthesis of pyrrolo[1,2-*a*]quinoxalines, we include methods based either on condensed derivatives of quinoxaline (a) or on compounds containing neither a pyrrole ring nor a quinoxaline system (b). In method (b), the pyrroloquinoxaline system can be formed with the initial formation of the pyrrole ring (b-*I*) or the quinoxaline system (b-*II*). In this review, we examine only the second version (b-*II*).

A typical example is the recyclization of isoxazolo[2,3-*a*]quinoxalines **95a–m** to pyrrolo[1,2-*a*]quinoxalines **96a–m** (Kim et al. 1989, 1990a, c), shown in Scheme 3.31.

Investigation of the decomposition of 2-azidophenazine **97a** in various hydrocarbon solvents showed that the main product in all the solvents at 130–131 °C is 2-aminophenazine **98** (Scheme 3.32). The same compound is readily obtained at room temperature in tetraline and decaline. In other solvents (hexane, cyclohexane, benzene, and xylene) saturated with oxygen, 2-nitrophenazine **99**, 3-[2-(3-formylquinoxalinyl)]acrylonitrile **100**, and 4-formyl-1-nitrosopyrrolo[1,2-*a*]quinoxaline **101** are formed, while in the absence of oxygen resinification occurs (Bettinetti et al. 1978).



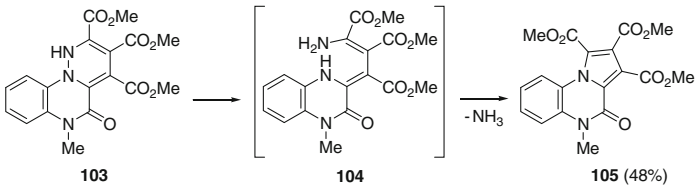
Scheme 3.32 The decomposition of 2-azidophenazine in various solvents



Scheme 3.33 The decomposition of 2-azido-1-methoxyphenazine in benzene

Under analogous conditions, 2-azido-1-methoxyphenazine **97b** forms the derivative of pyrrolo[1,2-*a*]quinoxaline **102**, but here the number of side products reaches six (Scheme 3.33) (Albini et al. 1987).

Another example of the modification of a tricyclic compound is the transformation of pyridazinoquinoxaline **103** in an acidic medium into the pyrroloquinoxaline **105** (Scheme 3.34) (Abbott et al. 1972).



Scheme 3.34 Acid-catalyzed transformation of pyridazinoquinoxaline into the pyrroloquinoxaline

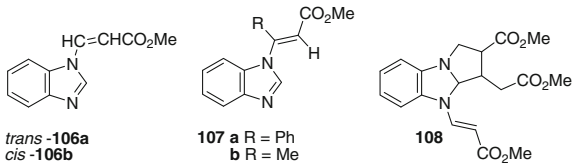
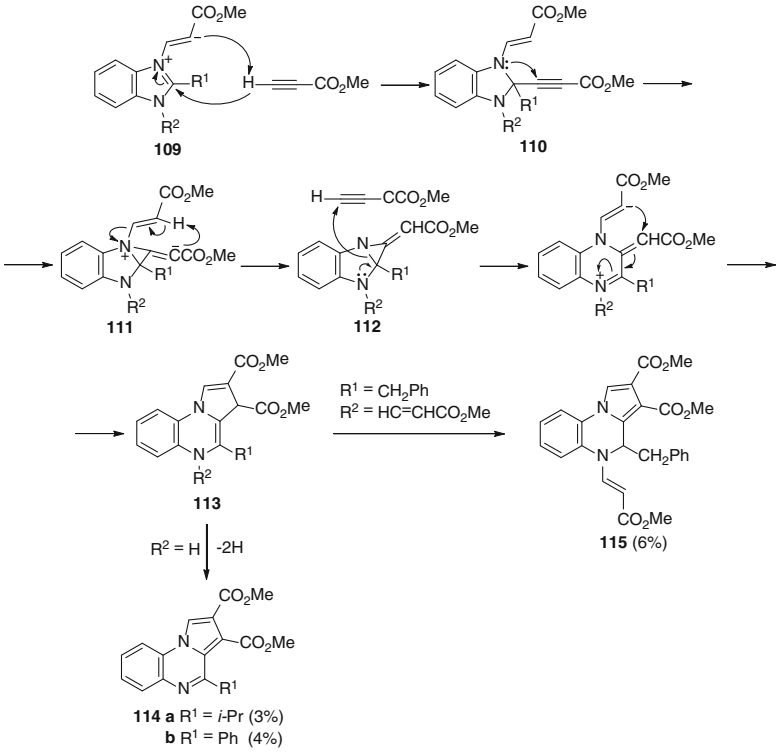
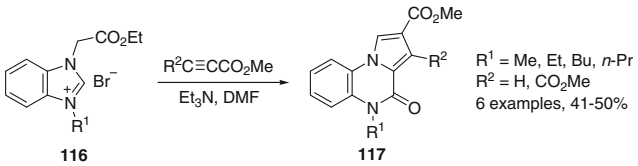


Fig. 3.5 Structures of the products of the reactions of methyl propargylate with benzylimidazole

The reaction of methyl propargylate (propiolate) with benzylimidazole and its 2-alkyl and aryl derivatives in acetonitrile leads to the formation of the methyl esters of 3-*trans*-(1-benzimidazolyl)acrylic acid **106a** and **107a**, **b**, whereas the reaction with benzimidazole in methanol leads exclusively to the corresponding *cis* isomer **106b**; in the absence of the solvent, the treatment of benzimidazole with methyl propiolate gives a mixture of compounds **106a**, **b,** and pyrrolo[1,2-*a*]benzimidazole **108** (Fig. 3.5). At the same time, the 2-isopropyl, 2-phenyl, and 2-benzyl derivatives of benzimidazole in reaction with methyl propiolate without a solvent form the pyrrolo[1,2-*a*]quinoxalines **114** and **115** (Scheme 3.35) (Acheson and Verlander 1973).



Scheme 3.35 The reactions of methyl propargylate with 2-substituted benzimidazoles



Scheme 3.36 The reactions of methyl propargylate with 2-substituted benzimidazoles

The formation of the pyrrolo[1,2-*a*]quinoxalines can be represented by various schemes; according to one of them the zwitterion **109**, formed under the reaction conditions from the corresponding benzimidazole derivative, detaches a proton from the methyl propriolate with the generation of an acetylide anion, which in turn adds to the benzimidazole at position 2. As shown in the scheme, nucleophilic attack by the nitrogen atom at the triple bond generates a new carbanion. *cis*-Elimination of methyl propiolate (of the Chugaev type) from the intermediate **111** leads to compound **112** and methyl propiolate, recombination of which leads to the structure **113**. Aromatization of compound **113** with R^1 = H or prototropic isomerization of the tricycle **113** with R^1 = $CH{=}CHCO_2Me$ gives compounds **114** and **115,** respectively (Acheson and Verlander 1973).

The benzimidazoles **116** are also transformed into pyrroloquinoxalines **117** by the action of acetylenecarboxylic acid derivatives (Scheme 3.36) (Meth-Gohn 1975; Rowland and Taylor 1979; Ager et al. 1988).

Economically favorable and ecologically harmless methods, which are in most cases one-pot tandem processes, occupy a special position among methods for the synthesis of condensed heterocyclic compounds.

As seen from the retrosynthetic analysis of the structure presented below, the simplest and most accessible reagent for the synthesis of pyrrolo[1,2-*a*]quinoxalines is 1,2-DAB. If the aim is to synthesize a derivative of pyrrolo[1,2-*a*]quinoxaline from 1,2-DAB, the second reagent must be a compound with at least five carbon atoms having functional centers capable of reacting with the amino groups of the 1,2 DAB at positions 1, 2, and 5 (Fig. 3.6).

Derivatives of 2-hydroxy-1,5-diketones **118a–d**, which are synthetic equivalents of synthon **F**, meet these requirements. The reaction of 2-hydroxy-1,5-diketones **118a–d** with 1,2-DAB leads to the formation of derivatives of 4,5-dihydropyrrolo [1,2-*a*]quinoxaline **119a**, **b**, which are dehydrogenated by the action of MnO_2 to the corresponding derivatives of pyrrolo[1,2-*a*]quinoxaline **120a**, **b**. The use of

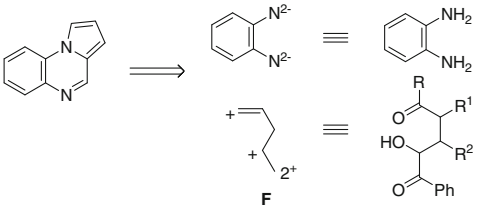
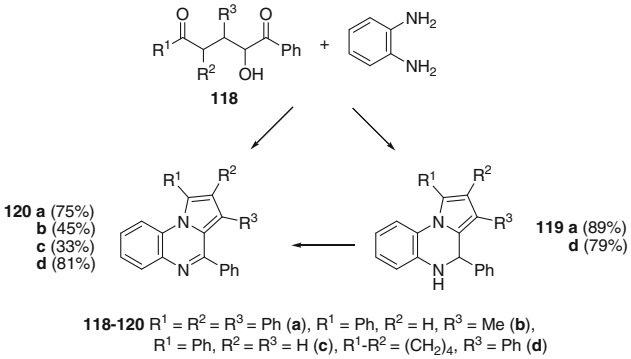


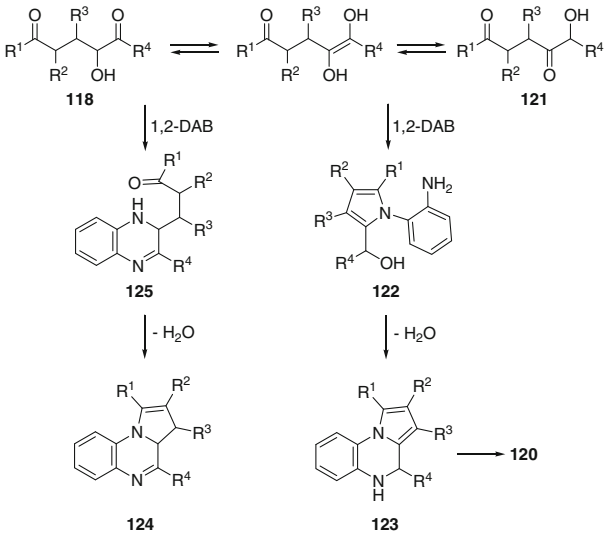
Fig. 3.6 Retrosynthetic analysis of the structure of pyrrolo[1,2-*a*]quinoxaline



Scheme 3.37 The reaction of 2-hydroxy-1,5-diketones with 1,2-DAB

2-hydroxy-1,5-diketones **118c**, **d**, however, leads directly to the formation of pyrrolo[1,2-*a*]quinoxalines **120c**, **d** (Scheme 3.37) (Kaminskii et al. 1992).

The formation of the pyrrolo[1,2-*a*]quinoxaline structure in this reaction can be represented in one of two ways (Scheme 3.38): (a) isomerization of the 2-hydroxy-1,5-diketone **118** to the 5-hydroxy-1,4-diketone **121** with the subsequent formation of the *o*-aminophenylpyrrole **122** and closure of the dihydroquinoxaline structure **123**; (b) reaction of the α-hydroxyketone fragment with 1,2-DAB with the formation of the hydroquinoxaline derivative **125** and subsequent closure of the dihydropyrrole ring and isomerization of the 3,3*a*-dihydropyrrolo[1,2-*a*]quinoxaline structure **124** to the more stable 4,5-dihydropyrrolo[1,2-*a*]quinoxaline structure **123**.



Scheme 3.38 Two pathways in the reaction of 2-hydroxy-1,5-diketone with 1,2-DAB

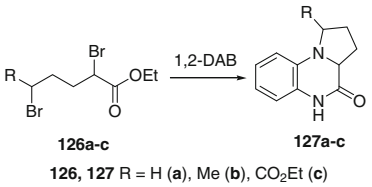
The second path seems more likely since during the reaction of the hydroxy-diketone with 1,2-DAB in a 15:1 mixture of ethanol and acetic acid and subsequent oxidation, a mixture of compound **120** and the quinoxaline derivative **125** in a ratio of 2:5 is formed.

The reaction of 1,2-DAB with the α,δ-dihalo carboxylic acids **126a–c** leads to annelation of the pyrrolo[1,2-*a*]pyrazine system and the formation of 1,2,3,4-tetrahydropyrroloquinoxalinones **127a–c** (Scheme 3.39) (Likhosherstov et al. 1968).

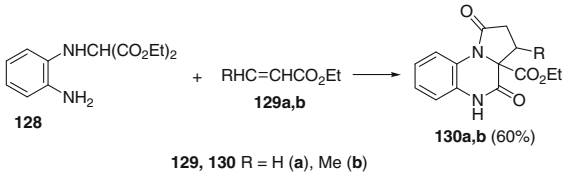
The authors of (Artico et al. 1967, 1968) described the construction of the tricycle **130a**, **b** as the result of condensation of the 1,2-DAB derivative **128** with the ethyl acrylates **129a**, **b** (Scheme 3.40).

The diethyl 5-hydroxy-6-oxotetrahydro-2*H*-pyran-2,3-dicarboxylate **131** is also converted by the action of 1,2-DAB into a derivative of pyrroloquinoxalines **132** (Scheme 3.41) (Kumashiro 1961).

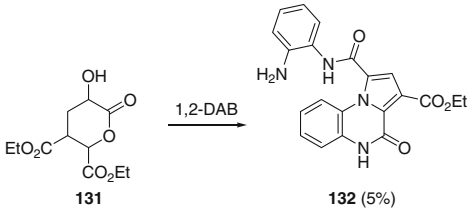
The *N*-oxides not only of quinoxalines but also of 1,4-benzodiazepines can serve as excellent 1,3-dipoles in the synthesis of derivatives of pyrrolo[1,2-*a*]quinoxalines. For example, the reaction of chlorodiazepineoxide **133** with dimethyl acetylenedicarboxylate takes place by a scheme of 1,3-dipolar addition with the



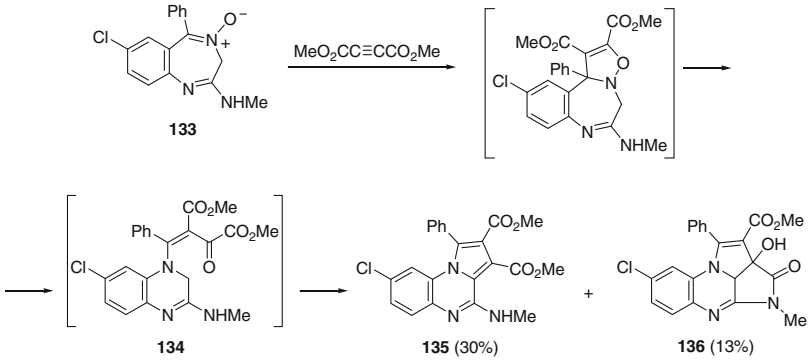
Scheme 3.39 The reaction of α,δ-dihalo carboxylic acids with 1,2-DAB



Scheme 3.40 Reaction diethyl 2-(2-aminophenylamino)malonate with ethyl acrylates



Scheme 3.41 Condensation of 5-hydroxy-6-oxotetrahydro-2*H*-pyrane with 1,2-DAB



Scheme 3.42 Condensation of chlorodiazepineoxide with dimethyl acetylenedicarboxylate

formation of two types of tri- and tetracyclic derivatives of pyrrolo[1,2-*a*]quinoxalines **135** and **136** (Scheme 3.42) (Miyadera et al. 1977). The intermediate formation of compound **134**, which is converted into compounds **135** and **136** as a result of intramolecular cyclocondensations, is explained by a Beckmann-type rearrangement in the adduct formed at the first stage of 1,3-cycloaddition.

3.1.12 Conclusion

According to the data in Table 3.1, of the 12 possible methods for the synthesis of pyrrolo[1,2-*a*]quinoxalines the most successful are the methods based on the **QA1**, **QB1**, **QC1**, **QC2**, and **QE2** approaches. Methods based on **QA2**, **QA3**, **QA4**, and **QB2** can only be realized after effective methods have been developed for the synthesis of *N*-alkylated derivatives of quinoxalines with alkyl fragments of various lengths and with various functional groups at the terminal atoms of the alkyl fragment that promote closure of the pyrrole ring, or with participation of the C(2) atom of the quinoxaline system, or with participation of the substituent at position 2 of the quinoxaline system.

Table 3.1 Possible and implemented methods of synthesis of pyrrolo[1,2-*a*]quinoxalines based on quinoxaline derivatives

Based on quinoxaline derivatives	
Possible	Implemented (number of papers)
QA1, **QA2**, **QA3**, **QA4**	**QA1** (16), **QA2** (0), **QA3** (0), **QA4** (0)
QB1, **QB2**, **QB3**	**QB1** (2), **QB2** (0), **QB3** (1)
QC1, **QC2**	**QC1** (16), **QC2** (5)
QD	**QD** (4)
QE1, **QE2**	**QE1** (1), **QE2** (6)
Other methods	(8)

3.2 Pyrrolo[l,2-*a*]quinoxalines Based on Pyrroles

3.2.1 Introduction

In a continuation of the previous Sect. 3.1, where possible methods for the construction of pyrrolo[1,2-*a*]quinoxalines based on quinoxalines were examined, data are presented here on methods of synthesis based on pyrroles and other systems that are not derivatives of either quinoxalines or pyrroles.

Various possible methods based on pyrroles for the construction of the pyrrolo [1,2-*a*]quinoxaline system are given below (Fig. 3.7).

3.2.2 Type PA1 Production Methods

A strategy for the synthesis of pyrrolo[1,2-*a*]quinoxalines based on pyrrole derivatives can be developed on the basis of the structural components used for the formation of the pyrazine ring. The principles represented by the symbol **PA1** originating from retrosynthetic analysis, i.e., the cyclocondensation of 1-aryl derivatives of pyrrole containing N-C fragments at the *ortho*-position of the aryl substituent, are most often used. An example of a synthesis using such an approach is the intramolecular cyclization of 1-(2-isocyanophenyl)pyrrole **137a**, which is easily obtained by dehydration of the corresponding formylamino derivative with a $POCl_3/Et_3N$ mixture in THF.

The reaction takes place in the presence of catalytic amounts of boron trifluoride etherate under mild conditions (CH_2CH_2, 0 °C), resulting in the formation of unsubstituted pyrrolo[1,2-*a*]quinoxaline **138** with an almost quantitative yield (Kobayashi et al. 1998, 2001a). The cyclization of compound **137** catalyzed by boron trifluoride etherate also goes well in the presence of various aldehydes and ketones (Kobayashi et al. 1998, 2001a), semiacetals (Kobayashi et al. 2001a), and 2,5-Diethoxytetrahydrofuran (Kobayashi et al. 2001a) and by the action of various epoxides (Kobayashi et al. 2001a); here, various derivatives of pyrrolo[1,2-*a*]

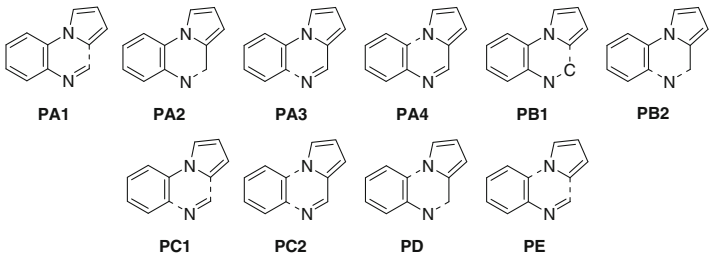
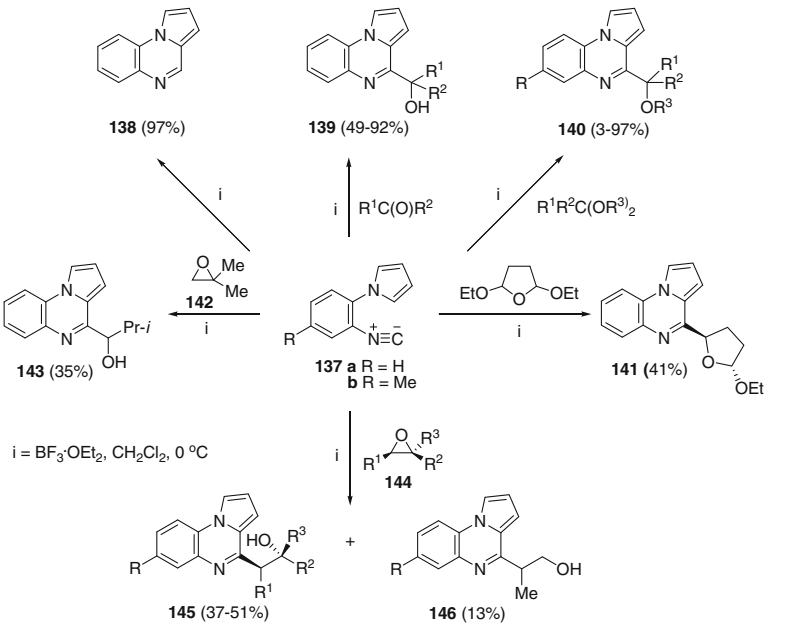


Fig. 3.7 Possible variants of the construction of the pyrrolo[1,2-*a*]quinazoline system on the basis of pyrroles



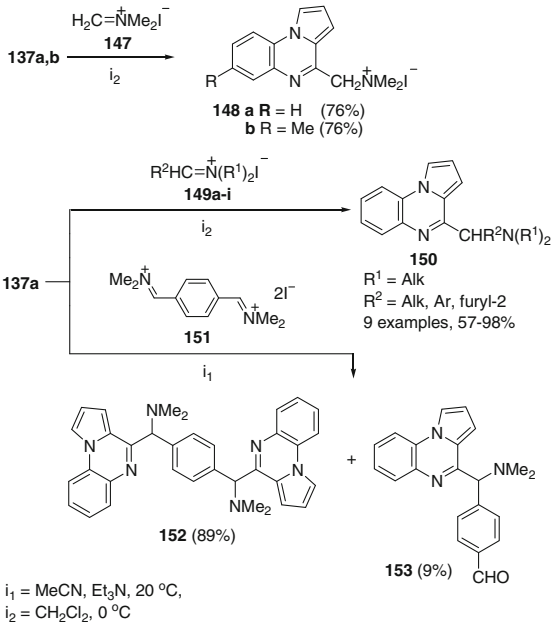
139 R^2 = H (**a-e**): R^1 = Et (**a**), *i*-Pr (**b**), CMe_2Et (**c**), Ph (**d**), furyl-2 (**e**); R^1 = R^2 = Me (**f**); R^1-R^2 = $(CH_2)_6$ (**g**); R^1 = Ph, R^2 = Me (**h**); R^1 = Me, R^2 = CO_2Et (**i**); R^1 = Me, R^2 = $(CH_2)_2CO_2Et$ (**j**)
140 R = R^2 = H, R^1 = R^3 = Me (**a**), R = R^2 = H, R^1 = Me, R^3 = Et (**b**), R = H, R^1 = R^2 = Me, R^3 = Et (**c**), R = R^2 = H, R^1 = vinyl, R^3 = Et (**d**), R = R^2 = H, R^1 = Ph, R^3 = Me (**e**), R = R^1 = Me, R^2 = H, R^3 = Et (**f**)
145 R = R^1 = R^2 = H, R^3 = Me (**a**), R = R^1 = R^2 = H, R^3 = Ph (**b**), R = R^3 = H, R^1-R^2 = $(CH_2)_4$ (**c**), R = R^1 = R^2 = H, R^3 = $(CH_2)_2CH{=}CH_2$ (**d**), R = Me, R^1-R^2 = $(CH_2)_4$ (**e**)
146 R = H (**a**), Me (**b**)

Scheme 3.43 Boron trifluoride etherate catalyzed cyclization of 1-(2-isocyanophenyl)pyrroles with various reagents

quinoxalines **138**–**141**, **143**, and **145** substituted at position 4 are formed with yields of 3–97 %, depending on the employed carbonyl component (Scheme 3.43) (Kobayashi et al. 1998, 2001a).

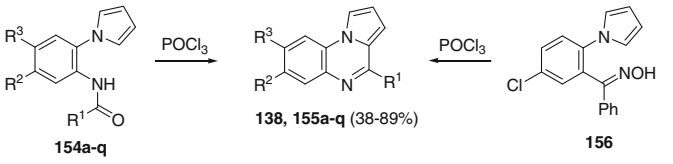
The reaction of 1-(2-isocyanoaryl)pyrroles with Eschenmoser's salt **147** also goes smoothly with the formation of dimethyl(pyrrolo[1,2-*a*]quinoxalin-4-ylmethyl)ammonium iodides **148** (Scheme 3.44), which after treatment with an aqueous solution of $NaHCO_3$ readily give quantitative yields of the free bases. In the case of the reactions of 1-(2-isocyanophenyl)pyrroles **137a**, **b** with other salts of the iminium type **149** and **151**, obtained from secondary amines and aldehydes in the presence of $Me_3SiCl/NaI/Et_3N$, it was shown that such a synthesis of 4-(1-dialkyl-aminoalkyl)pyrrolo[1,2-*a*]quinoxalines **150**, **152**, and **153** is universal (Kobayashi et al. 2001b).

During the construction of the pyrazine ring of the pyrrolo[1,2-*a*]quinoxaline system, the direct source of the N–C fragment can be not only an isocyano function ($-N^+{=}C^-$) but also an acylamino function (–NHC(O)R) (Cheeseman and Tuck



Scheme 3.44 Cyclization of 1-(2-isocyanophenyl)pyrroles with iminium salts

1965b, 1966; Garcia et al. 1968; Nagarajan et al. 1972; Kobayashi et al. 1998; Alleca et al. 2003; Guillon et al. 2007a). As a result, as far back as 1966, a general method was proposed for the production of pyrrolo[1,2-*a*]quinoxalines (Cheeseman and Tuck 1966) by the cyclization of 1-(2-aminophenyl)pyrroles, obtained by the Clauson-Kaas reaction (Clauson-Kaas and Tyle 1952), and their derivatives **154**. The cyclization of the acylamines **154** takes place during the action of phosphorus oxychloride (Scheme 3.45).



154, 155 $R^2 = R^3 = H$ (**a-d**): R^1 = Me (**a**), NHPh (**b**), Ph (**c**), CH_2Cl (**d**);
R^1 = Ph, R^2 = Cl, R^3 = H (**e**);
$R^2 = CF_3$, R^3 = H (**f-k**): $R^1 = CH_2Cl$ (**f**), *n*-Bu (**g**), $CH_2CH{=}CHMe$ (**h**), *n*-C_6H_{13} (**i**), $CH_2CH{=}CHPr$ (**j**), $(CH_2)_2C_6H_3(OCH_2O)$-3,4 (**k**);
R^2 = OMe, R^3 = H (**l-o**): R^1 = Me (**l**), *n*-Bu (**m**), *n*-C_6H_{13} (**n**), $CH_2CH{=}CHPr$ (**o**);
R^2 = H, R^3 = OMe (**p,q**): $R^1 = CH_2CH{=}CHMe$ (**p**), $CH_2CH{=}CHPr$ (**q**)
138 $R^1 = R^2 = R^3 = H$

Scheme 3.45 Cyclyzation of 2-(pyrrol-1-yl)benzanilides and benzophenone oxime when expoused to $POCl_3$

It was unexpectedly found (Garcia et al. 1968) that *o*-(pyrrol-1-yl)benzophenone oxime **156**, which undergoes a Beckmann rearrangement to 5-chloro-2-(pyrrol-1-yl)benzanilide **154e** during the action $POCl_3$ in DMF, can serve as a starting material for the production of the pyrroloquinoxaline **155e**. The structure of the pyrroloquinoxaline **155e** was confirmed unambiguously not only spectrally but also by an alternative synthesis from the authentic 5-chloro-2-(pyrrol-1-yl)benzanilide **154e** by the method in Scheme 3.45 (Cheeseman and Tuck 1966).

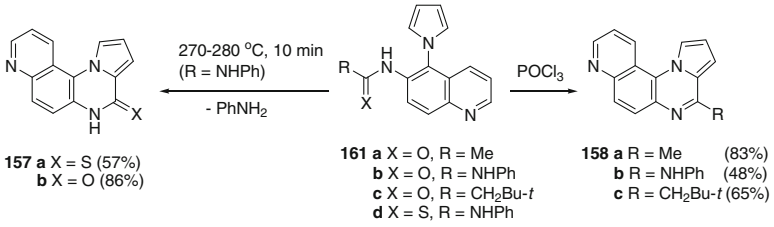
Similarly, condensed derivatives of pyrrolo[1,2-*a*]quinoxalines **157–160** were obtained from 5-(pyrrol-1-yl)-quinolines **161** (Scheme 3.46) (Lancelot et al. 1983a), 3-(pyrrol-1-yl)dibenzofurans **162** (Scheme 3.47) (Rault et al. 1979), and 3-(pyrrol-1-yl)carbazole **163** (Scheme 3.48) (Lancelot et al. 1984) containing at positions 6, 2, and 4, respectively, the functional group RC(X)NH, which was introduced by condensation of the corresponding amines with acetic anhydride, phenyl isocyanate, phenyl isothiocyanate, and aliphatic isothiocyanates.

Closure of the pyrazine ring in compounds **161a–c** is achieved by heating in the presence of $POCl_3$. Cyclization of compounds **161b**, **d** to pyrroloquinoxalines **157a**, **b** occurs in a boiling toluene solution for 1.5–2 h and during brief thermolysis, respectively (Scheme 3.46) (Lancelot et al. 1983a).

The pyrazine in 2-pyrrolyldibenzofyrans **162** is also formed by heating in the presence of $POCl_3$ (Scheme 3.47) (Rault et al. 1979).

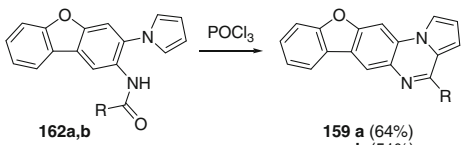
Closure of the pyrazine ring in the pyrrolylcarbazole **163** occurs during brief thermolysis at a temperature above 200 °C (Scheme 3.48) (Lancelot et al. 1984).

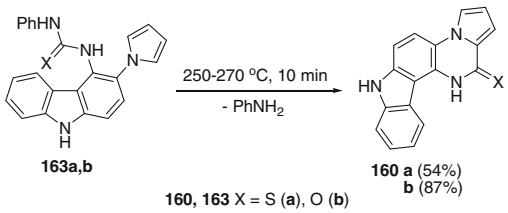
The cyclization of dimethyl [2-(pyrrol-1-yl)anilino]fumarate **165**, obtained by the reaction of *N*-(2-aminophenyl)pyrrole **164a** with dimethyl acetylenedicarboxylate for a week in boiling chloroform, leads to methyl 4-(2-methoxy-2-oxoethyl)pyrrolo[1,2-*a*]quinoxaline-4-carboxylate **167**. At the same time, diethyl



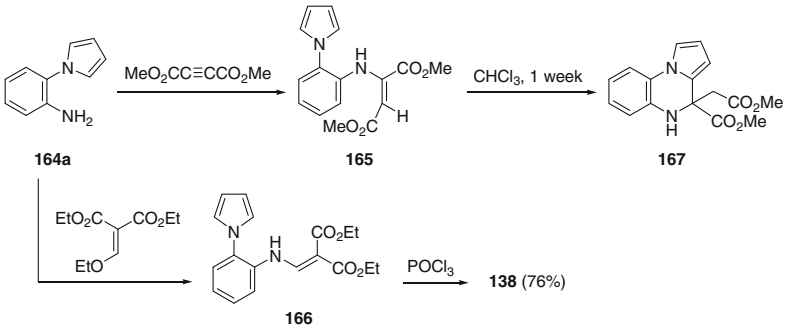
Scheme 3.46 Cyclization of the derivatives of 5-(pyrrol-1-yl)-quinolines under various conditions

Scheme 3.47 Cyclization of *N*-(3-(1*H*-pyrrol-1-yl)dibenzo[*b*,*d*]furan-2-yl)aceta- and benzamides when expoused to $POCl_3$





Scheme 3.48 Thermal cyclization of 1-(3-(1*H*-pyrrol-1-yl)-9*H*-carbazol-4-yl)-3-phenyl- thiourea and urea

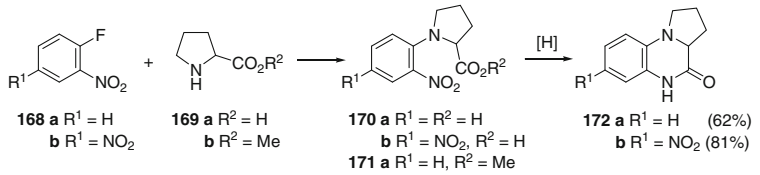


Scheme 3.49 Reactions of *N*-(2-aminophenyl)pyrrole with dimethyl acetylenedicarboxylate and diethyl ethoxymethylenemalonate

[2-(pyrrol-1-yl)anilino]methylenemalonate **166**, easily obtained from *N*-(2-aminophenyl)pyrrole **164a** in reaction with diethyl ethoxymethylenemalonate in boiling $POCl_3$, is transformed after 15 min into pyrrolo[1,2-*a*]quinoxaline **138** (Scheme 3.49) (Suschitzky et al. 1975).

3.2.3 Type PA2 Production Methods

There is only one method of realizing a synthesis of type **PA2**, and this involves reduction of the *N*-(2-nitrophenyl)pyrrolidine-2-carboxylic acids **170** or the esters of *N*-(2-nitrophenyl)pyrrole-2-carboxylic acid **171** (Scheme 3.50). Compounds **170** were obtained by the condensation of 1-fluoro-2-nitrobenzenes **168** with pyrrolidine-2-carboxylic acid **169a** or its ester **169b** (Adegoke and Babajide 1983; Abou-Gharbia et al. 1984; Freed and Abou-Gharbia 1984) in boiling ethanol in the presence of $NaHCO_3$. The reductive cyclization of compounds **170** and **171** was realized both with cyclohexene in boiling ethanol in the presence of 10 % Pd/C (Adegoke and Babajide 1983) and with iron powder in acetic acid (Abou-Gharbia

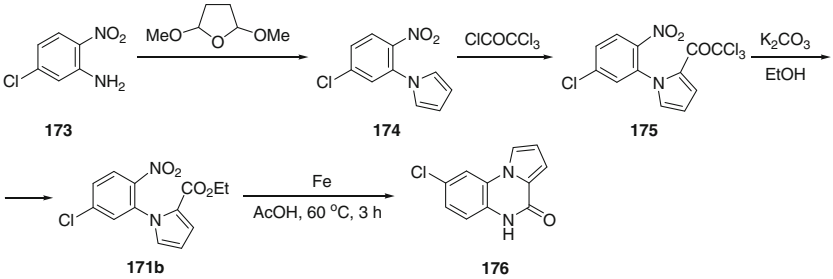


Scheme 3.50 Synthesis and cyclization of *N*-(2-nitrophenyl)pyrrolidine-2-carboxylic acid derivatives

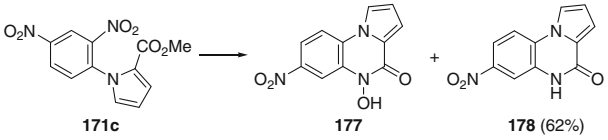
et al. 1984; Freed and Abou-Gharbia 1984) and also for compound **170a** with sodium dithionite in water (Abou-Gharbia et al. 1984).

A method for the synthesis of the derivative of *N*-(2-nitrophenyl) pyrrolidine-2-carboxylic acid **171b** involves alcoholysis of 1-(5-chloro-2-nitrophenyl)-2-trichloroacetyl-1*H*-pyrrole **175**, which is in turn obtained as a result of a two-stage process from 5-chloro-2-nitroaniline **173** (Silvestri et al. 2000). In this case, reductive cyclization is realized successfully with iron powder in acetic acid (60 °C, 3 h) (Scheme 3.51).

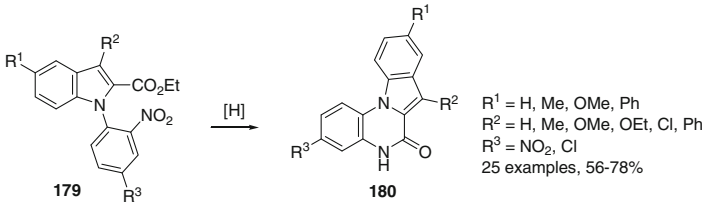
If ammonium sulfide is used as reducing agent, a mixture of tetrahydropyrroloquinoxaline **178** and the *N*-hydroxy derivative **177** is formed from the arylpyrrolidine **171c** (Scheme 3.52) (Chicharro et al. 2003).



Scheme 3.51 Synthesis and cyclization of ethyl 1-(5-chloro-2-nitrophenyl)-1*H*-pyrrole-2-carboxylate



Scheme 3.52 Cyclization of methyl 1-(2,4-dinitrophenyl)-1*H*-pyrrole-2-carboxylate



Scheme 3.53 Cyclization of ethyl 1-(2-nitrophenyl)-1*H*-indole-2-carboxylate derivatives

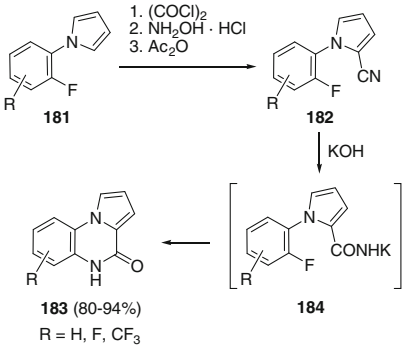
This approach has found use in the synthesis of condensed heterocyclic systems with a hydrogenated pyrrolo[1,2-*a*]quinoxaline fragment **180** (Scheme 3.53) (Merwade et al. 1990; Basanagoudar et al. 1991; Rajur et al. 1992).

3.2.4 Type PA3 Production Methods

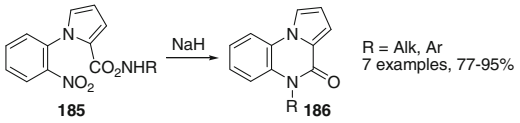
The key stage in the synthesis of pyrrolo[1,2-*a*]quinoxalines **183** (Scheme 3.54) by type **PA3** (Campiani et al. 1991, 1997) involves intramolecular substitution of a fluorine atom in the aromatic ring by the carboxamide group formed in situ in the 1-aryl-2-cyanopyrroles **182** by the action of KOH. The formation of compounds **182** is a multistage process: synthesis of the 1-arylpyrroles by the Clauson-Kaas reaction (Clauson-Kaas and Tyle 1952) and introduction of the CN group at position 2 of the pyrrole ring according to the Scheme 3.54.

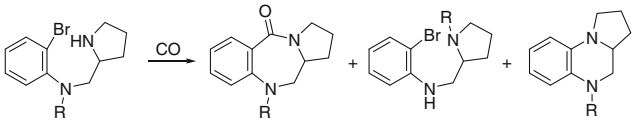
During the action of sodium hydride, substituted amides of pyrrolecarboxylic acids **185** undergo cyclization to 5-substituted pyrroloquinoxalin-4-ones **186** (Scheme 3.55) (Rotas et al. 2004).

Scheme 3.54 Synthesis and cyclization of 1-(2-fluorophenyl)-1*H*-pyrrole-2-carbonitrile derivatives



Scheme 3.55 Cyclization of 1-(2-nitrophenyl)-pyrrolecarboxylic acid derivatives





187a-d **188 a** (15%) **c** (26%) **d** (35%) **189 a** (14%) **b** (25%) **c** (9%) **190 a** (3%) **c** (5%) **d** (9%)

187-190 R = Ac (**a**), R = CHO (**b**), R = PhCO (**c**), R = $MeSO_2$ (**d**)

Scheme 3.56 Cyclization and rearrangement of 2-[*N*-*R*-*N*-(2-bromophenyl)aminomethyl]-pyrrolidines when exposed to carbon monoxide

3.2.5 *Type PA4 Production Methods*

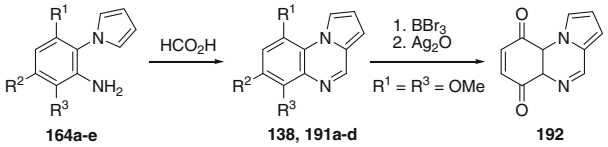
A special method for the synthesis of pyrrolo[1,2-*a*]quinoxalines using the **PA4** synthon has not been developed. However, during the production of pyrrolo-1,4-benzodiazepines by the insertion of carbon monoxide into 2-[*N*-*R*-*N*-(2-bromophenyl)aminomethyl]pyrrolidines **187** in the presence of catalytic amounts of $Pd(OAc)_2$ and PPh_3 pyrrolo[1,2-*a*]quinoxalines **190** were found together with other products formed as a result of the migration of, for example, an acyl group from the aniline nitrogen atom to the pyrrolidine nitrogen atom (Scheme 3.56) (Mory et al. 1984).

The structure and the mechanism of formation of the pyrroloquinoxaline **190** in this reaction were partly clarified by realizing closure of the ring in compound **187** in an atmosphere of argon in the absence of carbon monoxide. Moreover, it was shown that heating of compound **187** in an atmosphere of argon in the absence of the palladium catalyst also leads to a small yield of the pyrrolo[1,2-*a*]quinoxalines. The part played by the catalyst in the closure of the pyrazine ring is not understood.

3.2.6 *Type PB1 Production Methods*

An excellent example illustrating the production of pyrroloquinoxalines by the **PB1** path is the cyclization of 1-(2-aminophenyl)pyrroles with formic acid. Thus, boiling of compound **164a** in formic acid leads to the formation of unsubstituted pyrrolo [1,2-*a*]quinoxaline **138** with a yield of 80 % (Cheeseman and Tuck 1966; Gob and Cheeseman 1986). However, the reaction of the diaminophenylpyrrole **164e** under these conditions leads to the formation of 9-formyl-amidopyrroloquinoxaline **191d** (Scheme 3.57) (Hou and Balli 1992).

When an analogous strategy was used for the synthesis of pyrrolo[1,2-*a*] quinoxaline from 3,6-dimethoxy-2-nitroaniline, 6,9-dimethoxypyrrolo[1,2-*a*] quinoxaline **191c**, interesting in view of the presence of the methoxy groups, was obtained; under the right conditions, it was converted into 6,9-dihydroxypyrrolo [1,2-*a*]quinoxaline and pyrrolo[1,2-*a*]quinoxaline-6,9-dione **192** (Scheme 3.57).



164a-e **138, 191a-d** **192**

164 $R^1 = R^2 = R^3 = H$ (**a**); $R^1 = R^3 = H$, $R^2 = Me$ (**b**); $R^1 = R^3 = H$, $R^2 = Br$ (**c**); $R^1 = R^3 = OMe$, $R^2 = H$ (**d**); $R^1 = NH_2$, $R^2 = R^3 = H$ (**e**)
138 $R^1 = R^2 = R^3 = H$
191 $R^1 = R^3 = H$, $R^2 = Me$ (**a**); $R^1 = R^3 = H$, $R^2 = Br$ (**b**); $R^1 = R^3 = OMe$, $R^2 = H$ (**c**); $R^1 = NHC(O)H$, $R^2 = R^3 = H$ (**d**)

Scheme 3.57 Cyclization of 2-aminophenylpyrrole derivatives when exposed to formic acid oxidation one of their representatives

The heterocyclic quinone **192** can be used in the synthesis of more complex condensed systems by the Diels–Alder reaction with various dienes (Al-Sammerrai et al. 1980).

Methods for the synthesis of pyrrolo[1,2-*a*]quinoxalines based on 1-(2-aminophenyl)pyrroles began to develop after a more convenient and more effective method had been proposed for the production of the starting compound with an overall yield of 75 %; this involved reduction of the 1-(2-nitrophenyl) pyrrole obtained from *o*-nitroaniline and 2,5-diethoxytetrahydrofuran. The yield of 1-(2-aminophenyl)pyrrole from 1,2-DAB and tetrahydro-2,5-dipropoxyfuran amounts to only 40 %, and isolation of the reaction product involves prolonged steam distillation. The availability of compounds **164** made it possible to develop convenient methods for the synthesis of pyrrolo[1,2-*a*]quinoxalines on the basis of reactions with compounds that are synthetic equivalents of a synthon of the $R^1R^2CH^{2+}$ type. 1-(2-Aminophenyl)pyrrole reacts with benz-, anis-, and veratraldehydes in boiling ethanol with the formation of 4,5-dihydro-4-phenylpyrrolo [1,2-*a*]quinoxalines **194** with high yields (Scheme 3.58) (Cheeseman and Rafic 1971). The method was extended successfully to other aldehydes preferably containing electron-donating substituents and to cyclic ketones (cyclopentanone and cyclohexanone) and led to the production of pyrroloquinoxalines with yields from moderate to good depending on the nature of the carbonyl compound (Cheeseman and Rafic 1971; Raines et al. 1976; Szabo et al. 2009).

In spite of the fact that 1-(2-aminophenyl)pyrrole is considered as an excellent reagent in the synthesis of 4-substituted 4,5-dihydropyrrolo[1,2-*a*]quinoxalines, the

Scheme 3.58 Cyclization of 2-aminophenylpyrrole derivatives when exposed to carbonyl compounds

164 a $R^3 = H$
b $R^3 = Me$
f $R^3 = OMe$

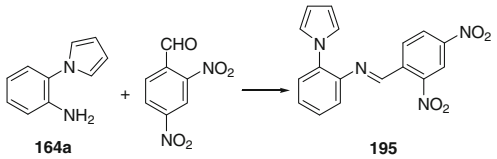
194
R^1 = H, Alk, Ar, Hetaryl
R^2 = H, CO_2Et, Ph
R^3 = H, Me, OMe
22 examples, 31-96%

possibility of using it depends largely on the nature of the carbonyl compound and the reaction conditions. The formation of 4,5-dihydropyrrolo[1,2-*a*]quinoxalines according to the schemes described above involves a reaction of the Mannich type, which requires a primary or secondary amine, an aldehyde (mostly formaldehyde), and a nucleophilic carbon atom. As a rule, the use of other active aldehydes in place of formaldehyde in the Mannich reaction sometimes does not lead to the desired results (Blicke 1942; Tramontini 1973). For this reason, the authors of (Abonia et al. 2001) attempted to extend the limits of the synthesis of pyrrolo[1,2-*a*] quinoxalines by using 1-(2-aminophenyl)pyrrole, which contains an amino group and a nucleophilic carbon atom at the same time. It was found that heating of a solution of compound **164** and the aldehydes **193** at 50 °C in ethanol in the presence of a catalytic amount of acetic acid led to 4,5-dihydropyrrolo[1,2-*a*] quinoxalines **194** with yields of 70–96 % irrespective of the nature of the employed aldehyde (Abonia et al. 2001). If aliphatic aldehydes such as isobutanal or undecanal are used, the formed 4,5-dihydropyrrolo[1,2-*a*]quinoxalines are gradually oxidized to pyrroloquinoxalines, and they were therefore characterized in the form of the *N*(5)-acyl derivatives. The mild conditions of the reaction (50 °C, a catalytic amount of acetic acid) guarantee widespread use of this method, although it is necessary to point out that 2,4-dinitrobenzaldehyde did not give the cyclization products under any conditions. The reaction resulted in the formation of Schiffs bases of type **195** even under very rigorous conditions (Scheme 3.59).

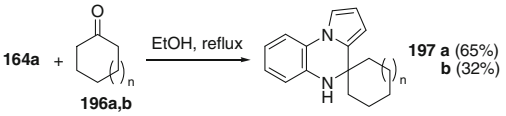
As reported (Raines et al. 1976), 2-aminophenylpyrrole **164a** when heated with cyclic ketones **196** in ethanol gave 4,5-dihydropyrrolo[1,2-*a*]quinoxalines **197** (Scheme 3.60).

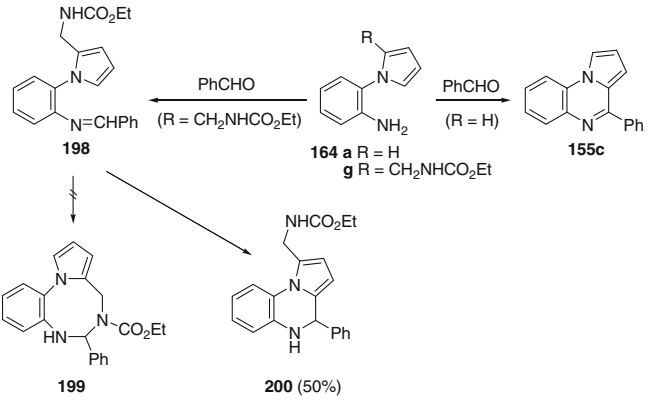
Cyclization in a basic medium also takes place in the case of the reaction of benzaldehyde with derivative of 1-(2-aminophenyl)pyrrole. For example, treatment of the aminoester **164g** with an equimolar amount of benzaldehyde in pyridine gives 4,5-dihydropyrrolo[1,2-*a*]quinoxaline **200** and not the expected pyrrolobenzotriazocine **199** (Korakas et al. 1996). The postulated intermediate in this reaction is probably the imine **198**. The reaction of compound **164a** with benzaldehyde in

Scheme 3.59 Reaction of 2-aminophenylpyrrole with 2,4-dinitrobenzaldehyde



Scheme 3.60 Reaction of 2-aminophenylpyrrole with cyclic ketones



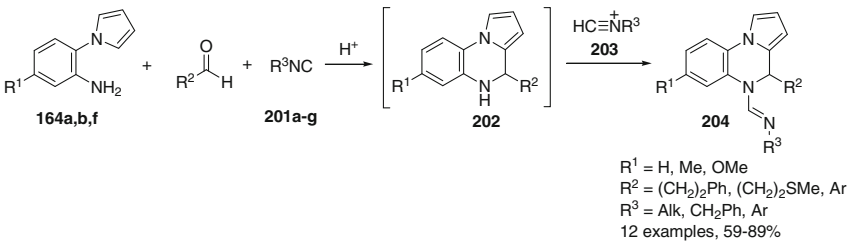


Scheme 3.61 Cyclization of 2-aminophenylpyrrole derivatives when exposed to benzaldehyde

the presence of copper acetate leads to 4-phenylpyrroloquinoxaline **155c** (Scheme 3.61).

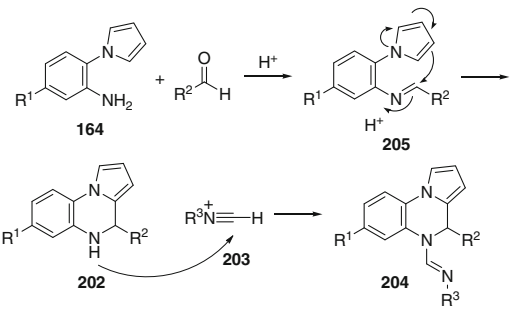
When the reactions of 1-(2-aminophenyl)pyrroles and aldehydes are carried out in the presence of isocyanides under acid-catalyzed conditions, the dihydropyrrolo [1,2-*a*]quinoxalines–amidines are obtained (Medda and Hulme 2014). The predominant pathway proceeds through the Pictet–Spengler reaction via **202**, which intriguingly is highly susceptible to the reaction with protonated isonitriles **203**, affording products of generic structure **204** in a single step. Enticingly, these new products contained three points of diversity, being derived from a novel, albeit unplanned, MCR containing an unexpected amidine functional group **204** (Scheme 3.62).

Scheme 3.63 depicts a proposed mechanism where amine **164** and aldehyde react to generate the expected Pictet–Spengler product **202** via the iminium species **205**. Evidence for the intermediate formation of **202** was observed through LC/MS monitoring, and the reaction with the protonated isonitrile **203** affords the final exocyclic amidine moiety **204**.



Scheme 3.62 Synthesis of dihydropyrrolo[1,2-*a*]quinoxalines–amidines via a Pictet–Spengler amidination sequence

Scheme 3.63 Proposed mechanism for the formation of dihydropyrrolo[1,2-*a*] quinoxalines–amidines

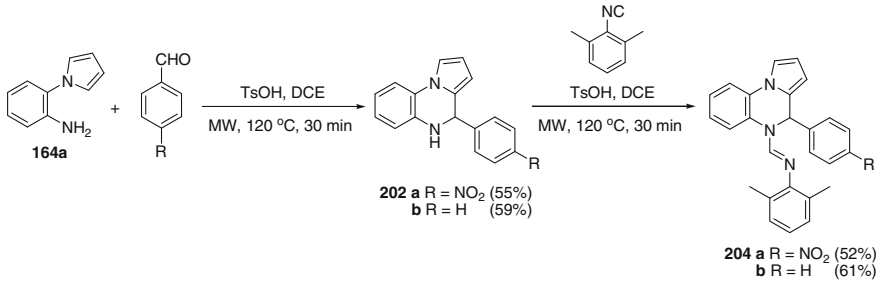


With an optimized procedure (microwave irradiation in DCE in the presence of TsOH (0.4 equiv) at 120 °C, for 30 min), the reaction scope was explored and 12 analogs **204**, (Scheme 3.62) prepared using three amines **164a**, **b**, **f**, seven aldehydes, and seven isonitriles **201** as reagents [Note: only three 1-(2-aminophenyl) pyrroles were found to be commercially available]. The one-pot procedure proved to be general, tolerating the full range of starting materials in high yield (39–89 %). As noted, the Pictet–Spengler intermediate was observed during reaction monitoring, and therefore two Pictet–Spengler intermediates, **202a** and **202b**, were isolated and treated with an isonitrile in the presence of para-toluene sulfonic acid at elevated temperatures in toluene. Final products **204a–b** were obtained in 52 and 61 % isolated yields, respectively (Scheme 3.64).

The synthesis of 3-(4-alkyl-4,5-dihydropyrrolo[1,2-*a*]quinoxalin-4-yl)-2*H*-chromen-2-one derivatives by a three-component reaction of salicylaldehyde, β-keto esters, and 1-(2-aminophenyl)pyrrole using piperidine–iodine as a dual system catalyst is reported (Table 3.2) (Alizadeh et al. 2014)

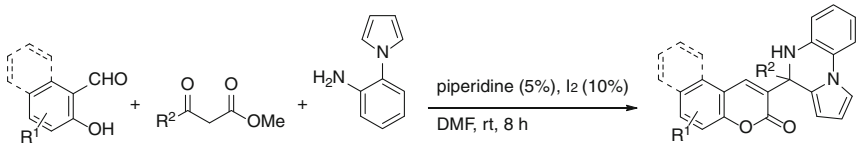
This reaction includes some important aspects like mild reaction condition, ease of handling, simple purification, and good to excellent yields.

If phosgene or triphosgene is used as the synthetic equivalent of the synthon R_2C^{2+} during construction of the pyrroloquinoxaline system from derivatives of 1-(2-aminophenyl)pyrrole 4,5-dihydropyrrolo[1,2-*a*]quinoxalin-4-ones **209** with a highly reactive carbamoyl function are formed. Syntheses of a series of functionally



Scheme 3.64 Two-step preparation of dihydropyrrolo quinoxaline amidines

Table 3.2 Synthesis of coumarin bearing pyrrolo[1,2-*a*]quinoxaline derivatives **208a–j**



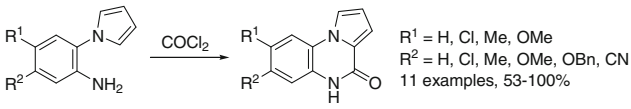
206 **207** **164a** **208a-j**

Entry	**206**	R^2	**208**	Yield (%)
1	Salicylaldehyde	Me	**208a**	75
2	5-Methylsalicylaldehyde	Me	**208b**	70
3	3-Methoxysalicylaldehyde	Me	**208c**	65
4	5-Methoxysalicylaldehyde	Me	**208d**	60
5	5-Nitrosalicylaldehyde	Me	**208e**	90
6	3,5-Dichlorosalicylaldehyde	Me	**208f**	95
7	2-Hydroxynaphthalene-1-carbaldehyde	Me	**208g**	83
8	Salicylaldehyde	*n*-Propyl	**208h**	70
9	3-Methoxysalicylaldehyde	*n*-Propyl	**208i**	68
10	2-Hydroxynaphthalene-1-carbaldehyde	*n*-Propyl	**208j**	60

substituted derivatives of pyrrolo[1,2-*a*]quinoxalines **209** of pharmacological interest by this method have been described (Scheme 3.65) (Nagarajan et al. 1972; Prunier et al. 1997; Campiani et al. 1999; Guillon et al. 2004, 2007a, b, 2008; Grande et al. 2007; Vidaillac et al. 2007; Desplat et al. 2008).

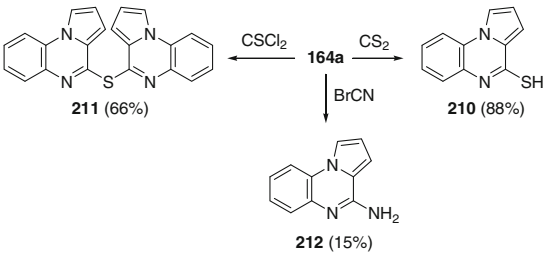
The reaction of aminophenylpyrrole **164a** with carbon disulfide in the presence of sodium hydroxide and with thiophosgene leads to 4-mercaptopyrroloquinoxaline **210** and to the sulfide **211,** respectively (Nagarajan et al. 1972; Guillon et al. 2007b), while reaction with BrCN in the presence of sodium carbonate leads to the formation of 4-aminopyrroloquinoxaline **212** (Scheme 3.66) (Nagarajan et al. 1972).

By extending the above-described method for the construction of the pyrrolo [1,2-*a*]quinoxaline system based on 1-(2-aminophenyl)pyrroles (Clauson-Kaas and Tyle 1952) to condensed heterocyclic systems containing vicinal amino groups in the benzene fragment it is possible to synthesize polycondensed heterocyclic systems with pyrrolo[1,2-*a*]quinoxaline structural fragments. For example, it was shown that three different pentacyclic condensed heterocyclic systems–derivatives of pyrrolopyrazinocarbazoles **160**, **216**, and **218** (Scheme 3.67) are formed,

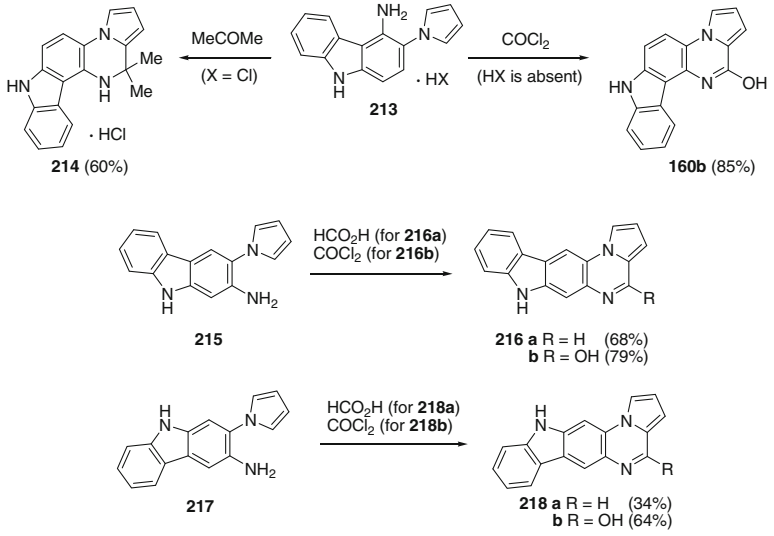


164 **209**

Scheme 3.65 Cyclization of 2-aminophenylpyrrole derivatives when exposed to phosgene



Scheme 3.66 Cyclization of 2-aminophenylpyrrole when exposed to thiophosgene, carbon disulfide, and cyanic bromide

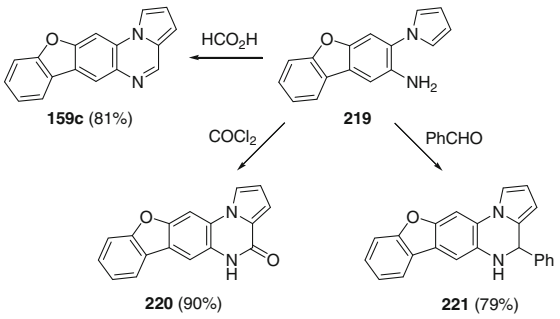


Scheme 3.67 Cyclization of the 4- and 2-amino-3-(pyrrol-1-yl)carbazoles and their isomeric 3-amino-2-(pyrrol-1-yl)carbazoles

depending on the nature of the source of the one-carbon fragment and the method of cyclization of the 4-amino-3-(pyrrol-1-yl)carbazole **213** and its isomeric 2-amino-3-(pyrrol-1-yl)- **215** and 3-amino-2-(pyrrol-1-yl)carbazoles **217** (Rault et al. 1979; Lancelot et al. 1983a, b, 1984).

When the same authors used the analogous strategy, functional derivatives of benzofuro[3,2-*g*]-pyrrolo[1,2-*a*]quinoxalines **159c**, **220**, and **221** were synthesized (Rault et al. 1979) based on 2-amino-3-(pyrrol-1-yl)dibenzofuran **219** (Scheme 3.68).

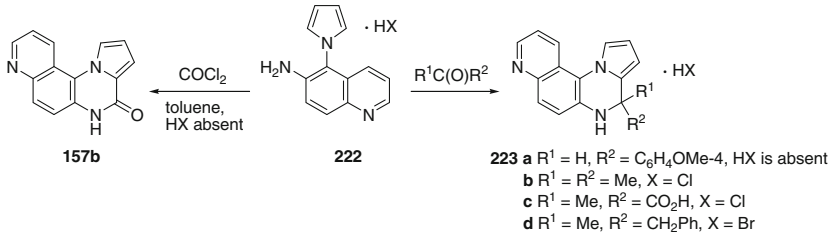
In a similar way, the authors of (Lancelot et al. 1983b) synthesized pyrido[2,3-*h*] pyrrolo[1,2-*a*]quinoxalines **223** and **157b** from the hydrohalide of 6-amino-5-(pyrrol-1-yl)quinoline **222**. The reactions of the 6-amino derivative **222** with



Scheme 3.68 Cyclization of 2-amino-3-(pyrrol-1-yl) dibenzofuran when exposed to formic acid, phosgene, and benzaldehyde

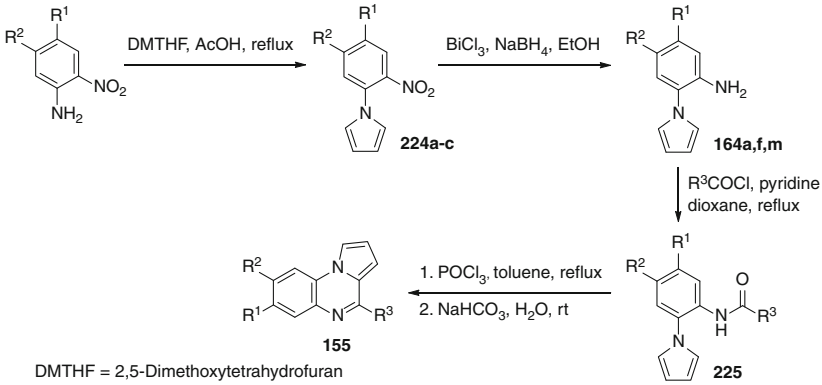
anisaldehyde and acetone under normal conditions and with pyruvic acid and with benzyl methyl ketone under the conditions of a Mannich condensation gave the corresponding 4,5-dihydroderivatives of pyrido[2,3-*h*]pyrrolo[1,2-*a*]quinoxalines **223** (Scheme 3.69) (Lancelot et al. 1983a).

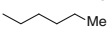
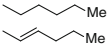
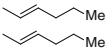
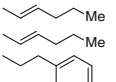
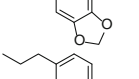
An original series of 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives, new structural analogs of *Galipea species* quinoline alkaloids, was synthesized from various substituted 2-nitroanilines via multistep heterocyclizations (Table 3.3) and tested for in vitro antiparasitic activity upon *Leishmania amazonensis* and *Leishmania infantum* strains (Guillon et al. 2007a). All 4-substituted pyrrolo[1,2-*a*] quinoxaline derivatives **155c**, **r**–**z**, **A**–**D** were obtained from 1-(2-aminophenyl) pyrroles **164a**, **f**, **m**. Preparation of the latter was performed in acetic acid according to the Clauson-Kaas reaction starting from 2-nitroanilines and 2,5-dimethoxytetrahydrofuran (DMTHF). The resulting 1-(2-nitrophenyl)pyrroles intermediates **224a**–**c** were subsequently reduced into the attempted 1-(2-aminophenyl)pyrroles **164a**, **f**, **m** using a $BiCl_3$–$NaBH_4$ treatment (Table 3.3). The commercially unavailable 5-methoxy-2-nitroaniline was prepared according to the literature (Kauffman et al. 1995; Zhang et al. 1996). The reaction of various alkyl-, alkenyl-, or aryl-acid chlorides with **164a**, **f**, **m** led to the acetamides **225a**–**n**. The 4-substituted pyrrolo[1,2-*a*]quinoxalines **155c**, **r**–**z**, **A**–**D** were prepared by cyclization of these amides **225a**–**n** in refluxing phosphorus oxychloride according to the Bischler–Napieralski reaction (Bischler and Napieralski 1893).



Scheme 3.69 Cyclization of 5-(1*H*-pyrrol-1-yl)quinolin-6-amine and its salts when exposed to phosgene and carbonyl compounds

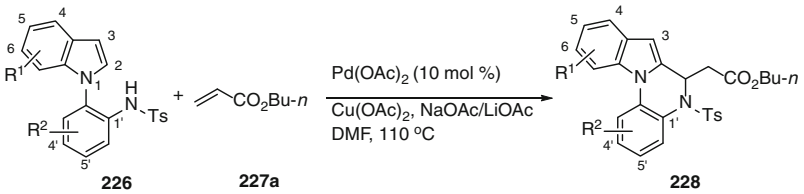
Table 3.3 Synthesis of 4-substituted pyrrolo[1,2-*a*]quinoxaline derivatives



Entry	R^1	R^2	R^3	**225**	Yield (%)	**155**	Yield (%)
1	H	H		**225a**	60	**155r**	78
2	OMe	H		**225b**	78	**155s**	50
3	H	H		**225c**	59	**155t**	23
4	OMe	H		**225d**	71	**155u**	16
5	H	OMe		**225e**	60	**155v**	22
6	H	H		**225f**	71	**155w**	61
7	OMe	H		**225g**	74	**155x**	93
8	H	H		**225h**	72	**155y**	54
9	OMe	H		**225i**	61	**155z**	37
10	H	OMe		**225j**	60	**155A**	26
11	H	H		**225k**	74	**155B**	77
12	H	H		**225l**	63	**155C**	70
13	H	H		**225m**	79	**155D**	48
14	H	H		**225n**	71	**155c**	53

An efficient Pd-catalyzed highly regioselective C–H olefination and cyclization sequence of *N*-aryl-substituted indoles and electron-withdrawing olefins has been developed (Wang et al. 2012). The reaction is applicable to a wide range of substrates with various functional groups affording the corresponding indole/pyrrole-fused quinoxaline derivatives in moderate to good yields. As summarized in Table 3.4, a number of alkyl and alkyoxyl substituents can be incorporated on the indole or benzene ring at various positions without significant loss in reaction efficiency (entries 2–6 and 9–10, $R^{1,2}$ = Me, MeO, or BnO). As revealed in entries 7 and 12, fluoro-substituted substrates in this cascade reaction have been successfully utilized (Shimizu and Hiyama 2005; Müller et al. 2007; Nie et al. 2011). Of note, a chloro group on the indole or phenyl ring of the substrate, which

Table 3.4 Pd-catalyzed C–H olefination/cyclization sequence



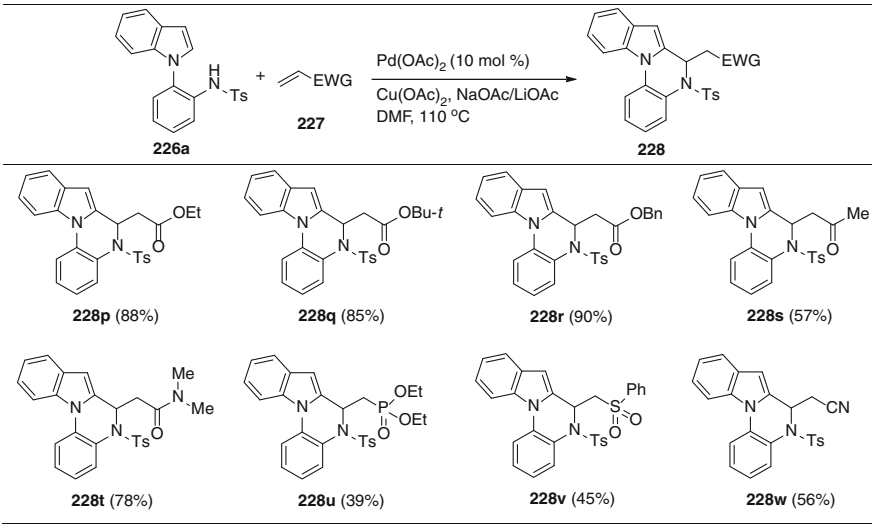
226 **227a** **228**

Entry	**226**	R^1	R^2	**228**	Yield (%)
1	**226a**	H	H	**228a**	82
2	**226b**	Me-4	H	**228b**	80
3	**226c**	Me-5	H	**228c**	81
4	**226d**	Me-6	H	**228d**	88
5	**226e**	BnO-5	H	**228e**	71
6	**226f**	$(MeO)_2$-5,6	H	**228f**	88
7	**226g**	F-6	H	**228g**	75
8	**226h**	Cl-6	H	**228h**	90
9	**226i**	H	Me-4	**228i**	87
10	**226j**	H	Me_2-4,5	**228j**	82
11	**226k**	H	Cl-4	**228k**	68
12	**226l**	H	CF_3-4	**228l**	66
13	**226m**	H	CO_2Me-4	**228m**	65
14	**226n**	Cl-6	Me-4	**228n**	73
15	**226o**	Me-3	H	**228o**	83

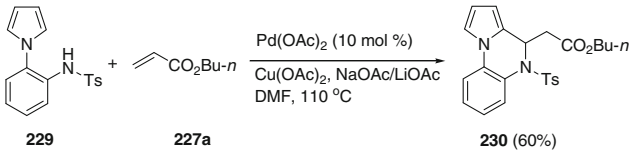
was well-tolerated in the current reaction system (entries 8 and 9). Notably, the catalytic system proved to be tolerant of valuable electrophilic functional groups, such as esters (entry 13). Additionally, the current catalytic system was not restricted to the use of monosubstituted substrates, but also allowed for efficient oxidative cyclization of different disubstituted *N*-arylation of indoles (entries 6 and 14). Perhaps more importantly, substrate **226o** not only demonstrated that steric interactions were well-tolerated but also showed excellent regioselectivity in our cascade catalytic system (entry 15).

Subsequently, a variety of electron-deficient terminal alkenes were examined. Scheme 3.70 shows that reactions of *N*-aryl-substituted indole **226a** with several acrylates **227p–w** preceded smoothly and efficiently to produce the corresponding products in generally good yields. Methyl vinyl ketone **228s** and *N,N*-dimethylacrylamide **228t** were also found to be competent coupling partners. Other olefins, such as vinyl sulfone, vinyl phosphonate, and vinyl cyanide, could also participate in this C–H olefination/cyclization sequence, albeit with poor reactivity.

Interestingly, it was found that the indole core could be successfully extended to pyrrole-derived systems. For example, *N*-aryl-substituted pyrrole **229** smoothly reacted with *n*-butyl acrylate **227a** affording the corresponding cyclized product in 60 % yield (Scheme 3.71).



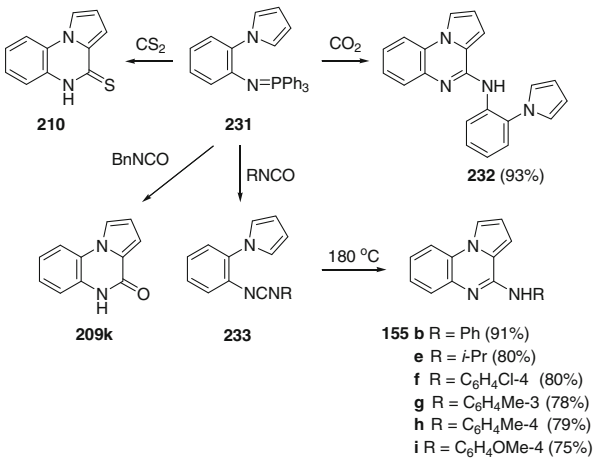
Scheme 3.70 Pd-catalyzed C–H olefination/cyclization sequence



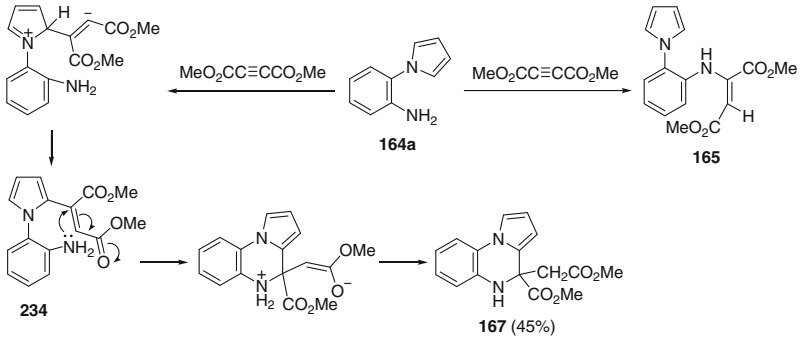
Scheme 3.71 Pd-catalyzed C–H olefination/cyclization sequence reaction of a pyrrole

Various heterocumulenes can be used as synthetic equivalents of the RC^{3+} synthon. In reaction with isocyanates, isothiocyanates, carbon dioxide, or carbon disulfide by the Wittig reaction, the iminophosphates **231**, obtained from *o*-(1-pyrrolyl)phenyl azide, form *o*-pyrrolylphenylheterocumulenes, which undergo cyclization to condensed pyrroloquinoxalines **155**, **209k**, **210**, and **232** (Scheme 3.72) (Molina et al. 1989, 1990).

The reaction of 1-(2-aminophenyl)pyrrole **164a** with dimethyl acetylenedicarboxylate, which acts as provider of the one-carbon fragment in the construction of the pyrrolo[1,2-*a*]quinoxaline system, takes place in chloroform for 36 h with the formation of the pyrroloquinoxaline **167** (yield 45 %) and dimethyl 2-(pyrrol-1-yl)-anilinofumarate **165** (yield 40 %). Compound **167** could be formed from dimethyl fumarate as a result of an intramolecular ene cyclization. In fact, such a transformation was observed, but before completion it required boiling of compound **165** in chloroform for a week. However, it should be noted that an amount of compound **167** detectable by spectral methods is formed after brief heating of the reaction mixture. It is not, therefore, impossible that part of compound **167** is formed according to the scheme presented below (Scheme 3.73) (Suschitzky et al. 1975).



Scheme 3.72 Cyclization of iminophosphates when exposed to carbon disulfide, carbon dioxide, and isocyanates

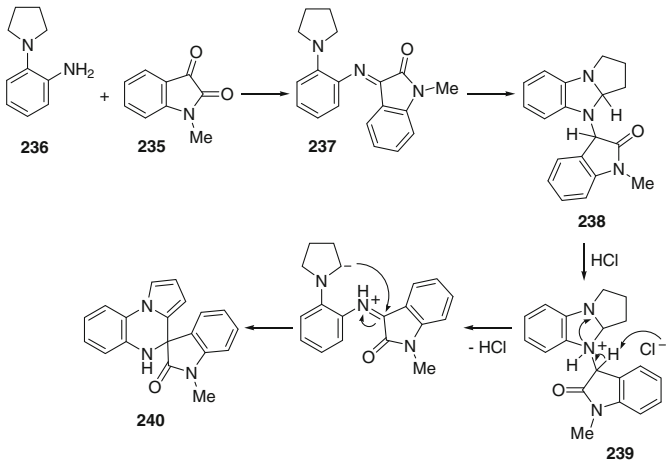


Scheme 3.73 Cyclization of 1-(2-aminophenyl)pyrrole when exposed to dimethyl acetylenedicarboxylate

N-Methylisatin **235** can also be used as a one-carbon fragment that reacts with 1-(2-aminophenyl)tetrahydropyrrole **236** in ethanol in the presence of conc. HCl with closure of the pyrazine ring according to the scheme presented below (Scheme 3.74) (Grantham and Meth-Cohn 1968).

It was shown experimentally that whereas the first two stages of the reaction (the formation of the Schiffs base **237** and the benzimidazole derivative **238**) can take place in the absence of hydrochloric acid, the presence of the acid is necessary for enlargement of the imidazole ring to a pyrazine ring according to a scheme analogous with the Stevens rearrangement.

A $PtCl_4$–catalyzed hydroamination-triggered cyclization strategy to access biologically interesting *N*-containing heterocycles such as pyrrolo[1,2-*a*]quinoxalines,

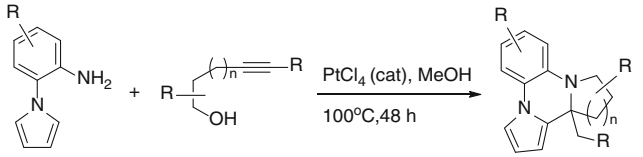


Scheme 3.74 Cyclization of 1-(2-aminophenyl)pyrrole when exposed to 1-methylindoline-2,3-dione

indolo[1,2-*a*]quinoxalines, and indolo[3,2-*c*]quinolines has been described (Patil et al. 2010a). The reaction of 1-(2-aminophenyl)pyrroles with alkynols were studied and the results are outlined in Table 3.5. Treatment of **164a** with 3-pentyn-1-ol **241b** in the presence of 5 mol % of $PtCl_4$ in methanol at 100 °C gave pyrrolo[1,2-*a*] quinoxalines **242a** in a 75 % yield (entry 1). Methyl-substituted 1-(2-aminophenyl) pyrroles also reacted well with **241a**, for this cascade transformation, to give **242b** and **242c** in good yields (entries 2 and 3). The alkynols **241c**, **241d**, and **241e** on reaction with **164a** gave the expected products **242d**, **242e**, and **242f** in 65, 59, and 55 % yields, respectively (entries 4, 5, and 6). As can be judged from entries 7–10, electron withdrawing and donating groups as well as chloro substituents in 2-aminophenylpyrroles were all well tolerated. The internal alkynes such as 3-hexyn-1-ol **241f** and 3-decyn-1-ol **241g** on reaction with **164a** gave **242k** and **242l** in 68 and 74 % yields, respectively (entries 11 and 12). 5-Hexyn-1-ol **241h** on reaction with **164a** gave **242m** in a 71 % yield (entry 13).

The scope of the hydroamination-triggered cyclization was extended to the synthesis of fused indolo[1,2-*a*]quinoxalines. As outlined in Table 3.6, it can be seen that a wide range of substituents on *N*-(2-aminophenyl)indoles reacted well to furnish the desired products **244a–i** in moderate to high yields (59–70 %). Particularly noteworthy is the fact that electron-withdrawing and donating substituents on the aromatic rings were not detrimental to the reactivity as $–CO_2Me$, –OMe, and –Cl groups were all well tolerated (entries 5, 6, and 7). Similarly, various fused indolo[3,2-*c*]quinolines **246a–k** were obtained from 2-(2-aminophenyl)indoles **245** and alkynols **241**, regardless of the electronic nature of the aromatic rings, in yields ranging from 59 to 85 % (Table 3.7, entries 1–12). However, unlike previous cases, the reaction between **245a** and 5-hexyn-1-ol 2 h under the established conditions did not give the desired product **246l** (entry 13).

Table 3.5 Hydroamination-triggered cyclization strategy for the synthesis of fused pyrrolo[1,2-*a*] quinoxalines



164a,f,k, o-r **241a-h** **242a-m**

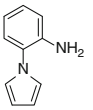
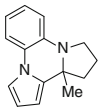
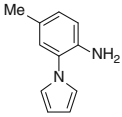
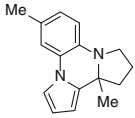
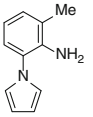
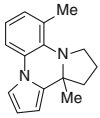
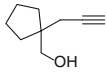
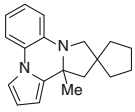
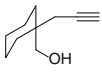
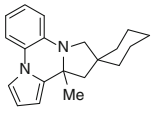
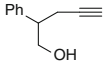
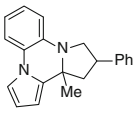
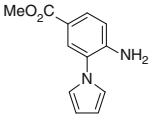
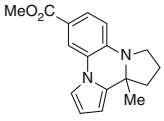
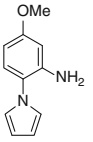
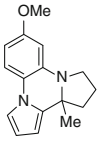
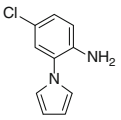
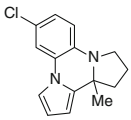
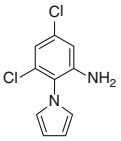
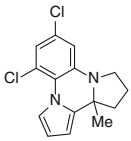
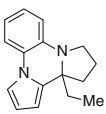
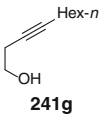
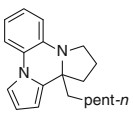
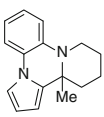
Entry	164	241	242	Yield (%)
1	 **164a**	 **241b**	 **242a**	75
2	 **164o**	 **241a**	 **242b**	69
3	 **164p**	**241a**	 **242c**	60
4	**164a**	 **241c**	 **242d**	65
5	**164a**	 **241d**	 **242e**	59
6	**164a**	 **241e**	 **242f**	55
7	 **164q**	**241a**	 **242g**	72
8	 **164f**	**241a**	 **242h**	76

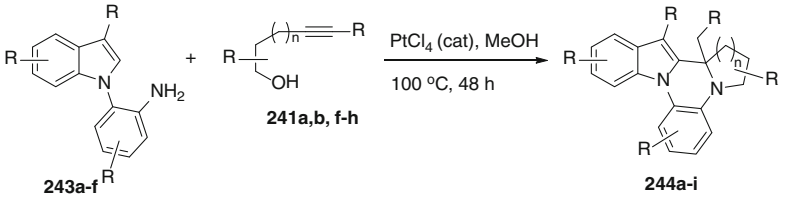
Table 3.5 (continued)

9	 **164k**	**241a**	 **242i**	75
10	 **164r**	**241a**	 **242j**	67
11	**164a**	 **241f**	 **242k**	68
12	**164a**	 **241g**	 **242l**	74
13	**164a**	 **241h**	 **242m**	71

We were pleased to find out that symmetrical diamines **247a**, **247b**, and **247c** on reaction with **241a**, under $Ph_3PAuOTf$ catalysis (the latter was found to be superior compared to $PtCl_4$ for this multicatalytic process), gave corresponding indolo[3,2-*c*] quinolines **246a**, **246b**, and **246f** in 60, 59, and 51 % yields, respectively (Scheme 3.75). It is worth mentioning that this process involving multiple catalytic cycles (Wasilke et al. 2005), assisted by a single metal catalyst, involves the formation of four bonds, that is, two C–C and two C–N bonds.

A plausible mechanism for this multicatalytic process is described using **247a** and **241a** as examples (Scheme 3.76) (Patil et al. 2010a). In essence, a total of four catalytic cycles **A** (hydroalkoxylation) (Chaudhuri and Kundu 2000; Pale and Chuche 2000; Peng and Ding 2003, 2005; Barluenga et al. 2005; Liu et al. 2005; Genin et al. 2006; Harkat et al. 2007, 2008), **B** (hydroamination) (Iritani et al. 1988; Arcadi et al. 1989, 2004; Rudisill and Stille 1989; Cacchi et al. 1994; McDonald and Chatterjee 1997; Kondo et al. 2001; Hiroya et al. 2002, 2004; Sakai et al. 2004, 2008; Li et al. 2005; Alfonsi et al. 2005; Hiroya et al. 2005; Zhang et al. 2007; Ambrogio et al. 2007; Trost and McClory 2007; Okuma et al. 2009), **C** (coupling), and **D** (dehydrative cyclization) were proposed. As shown in catalytic cycle **A**, the complexation of metal catalyst to the alkyne function in **241a** would lead to

Table 3.6 Hydroamination-triggered cyclization strategy for the synthesis of fused indolo[3,2-*a*] quinolines



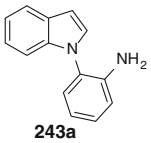
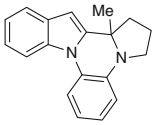
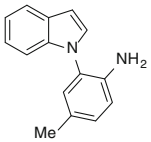
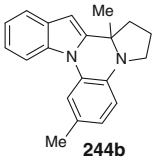
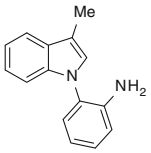
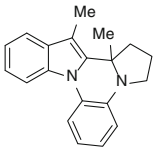
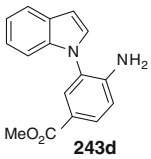
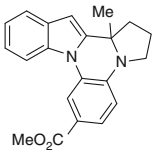
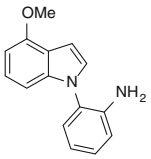
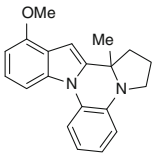
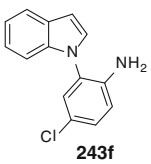
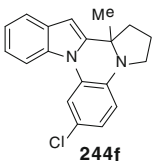
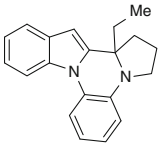
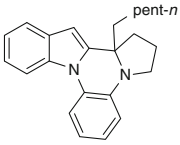
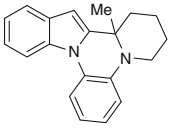
Entry	243	241	244	Yield (%)
1	 **243a**	**241a**	 **244a**	65
2	**243a**	**241b**	**244a**	63
3	 **243b**	**241a**	 **244b**	60
4	 **243c**	**241a**	 **244c**	70
5	 **243d**	**241a**	 **244d**	69
6	 **243e**	**241a**	 **244e**	59
7	 **243f**	**241a**	 **244f**	67

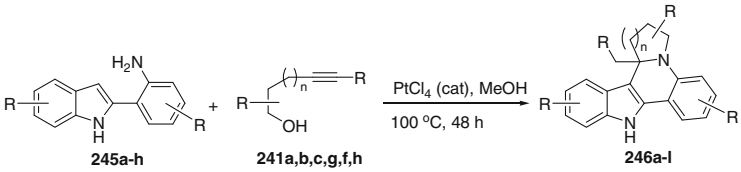
Table 3.6 (continued)

8	**243a**	**241f**	 **244g**	61
9	**243a**	**241g**	 **244h**	59
10	**243a**	**241h**	 **244i**	62

intermediate **248**. The cyclization step may then occur directly by the attack of the proximal hydroxyl group leading to vinylmetal (Hashmi et al. 2009) intermediate **249**, which on protonation and regeneration of catalyst would afford 2-methylenetetrahydrofuran **250**. At the same time, 2-aminophenylindole **245a** would be generated by intramolecular hydroamination of alkynylamine **247a** via intermediates **251** and **252** (cycle **B**). As described in cycle **C**, the metal complex catalyzes the formation of oxonium ion **253** from 2-methylenetetrahydrofuran **250**. The intermolecular nucleophilic addition of the indole **245a** to **253** might result in the formation of metal-coordinated *N,O*-ketal **254** from which the formal hydroaminationhydroarylation product **255** (vide infra) was obtained with regeneration of a catalyst. The compound **255**, thus obtained, would undergo dehydrative cyclization, under the catalysis of $PtCl_4$, to afford fused indolo[3,2-*c*]quinolines **246a** (cf. **256** and **257**, cycle **D**).

On the basis of the well-known literature data (Iritani et al. 1988; Arcadi et al. 1989, 2004; Rudisill and Stille 1989; Cacchi et al. 1994; McDonald and Chatterjee 1997; Chaudhuri and Kundu 2000; Pale and Chuche 2000; Kondo et al. 2001; Hiroya et al. 2002, 2004; Peng and Ding 2003, 2005; Sakai et al. 2004, 2008; Barluenga et al. 2005; Liu et al. 2005; Li et al. 2005; Alfonsi et al. 2005; Hiroya et al. 2005; Genin et al. 2006; Harkat et al. 2007, 2008; Zhang et al. 2007; Ambrogio et al. 2007; Trost and McClory 2007; Okuma et al. 2009) and based on own work (Patil et al. 2009, 2010b, c), earlier the authors propose that cycles **A** and **B** are catalyzed by $PtCl_4$. To examine the involvement of HCl in cycle **C**, a controlled experiment was performed with 2-*tert*-butylimino-2-diethylamino-1,3-dimethylperhydro-1,3,2-diazaphosphorine (BEMP) as a proton scavenger

Table 3.7 Hydroamination-triggered cyclization strategy for the synthesis of fused indolo[1,2-*a*] quinolines



245a-h **241a,b,c,g,f,h** **246a-l**

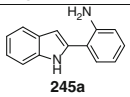
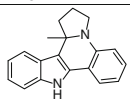
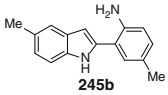
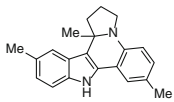
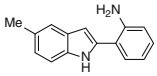
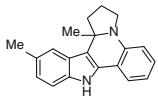
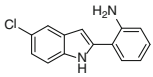
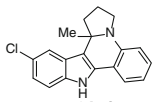
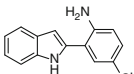
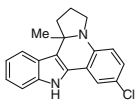
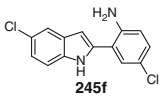
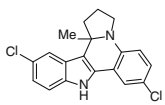
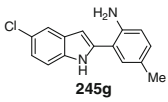
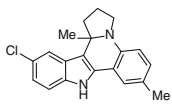
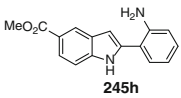
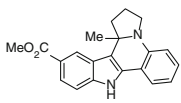
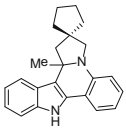
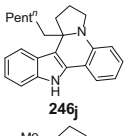
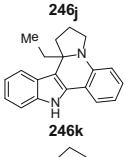
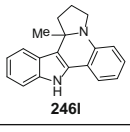
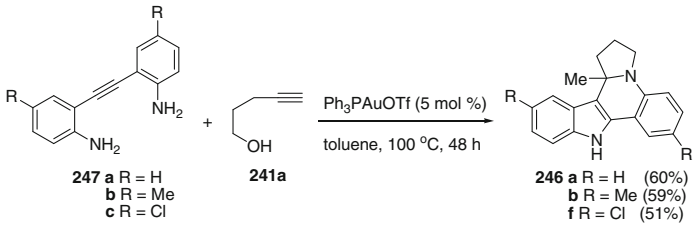
Entry	245	241	246	Yield (%)
1	 **245a**	**241a**	 **246a**	81
2	**245a**	**241b**	**246a**	73
3	 **245b**	**241a**	 **246b**	83
4	 **245c**	**241a**	 **246c**	85
5	 **245d**	**241a**	 **246d**	81
6	 **245e**	**241a**	 **246e**	63
7	 **245f**	**241a**	 **246f**	71
8	 **245g**	**241a**	 **246g**	67
9	 **245h**	**241a**	 **246h**	59

Table 3.7 (continued)

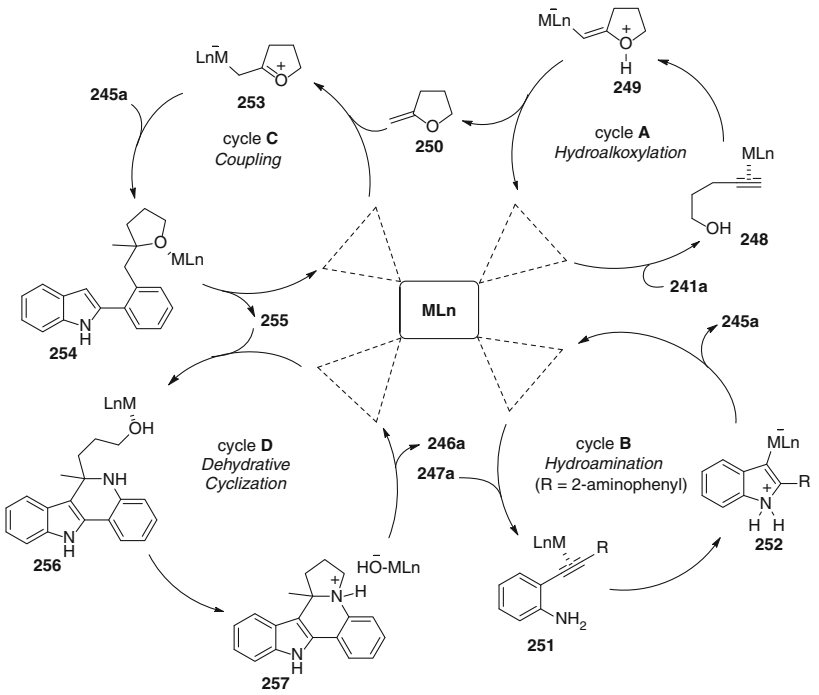
10	**245a**	**241c**	 **246i**	65
11	**245a**	**241g**	 **246j**	69
12	**245a**	**241f**	 **246k**	77
13	**245a**	**241h**	 **246l**	0



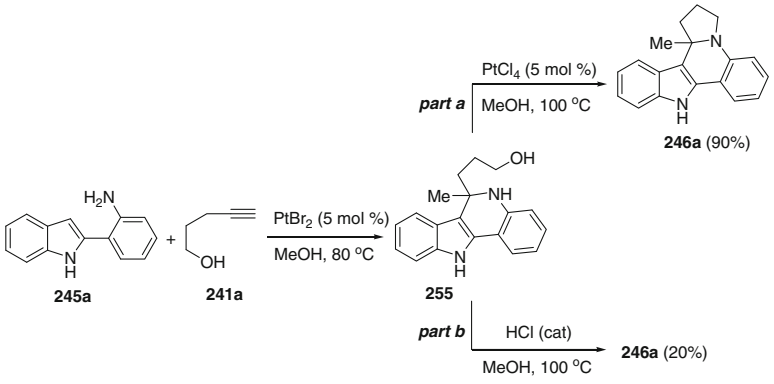
Scheme 3.75 Synthesis of fused indolo[3,2-*c*]quinolines starting directly from **247** and **241a**

(Yang et al. 2007; Barluenga et al. 2009). When **164a** was treated with **241a** in the presence of 5 mol % of $PtCl_4$ and 2 mol % of BEMP in MeOH at 100 °C for 48 h, **242a** was obtained, albeit in a 15 % yield. This suggests that the residual HCl is not responsible for cycle **C** (Ishihara et al. 2002). To determine the role of HCl as a catalyst in cycle **D**, a few control experiments were conducted (Scheme 3.77).

The hydroamination–hydroarylation product **255** was prepared from **245a** and **241a** by using Pt(II)-catalyzed procedure (Patil et al. 2009). The product **255**, thus obtained, when treated with $PtCl_4$ in methanol at 100 °C afforded the desired product in a 90 % yield (path *a*). On the other hand, using a catalytic amount of HCl, product **246a** was obtained in only 20 % yield under the same reaction conditions (path *b*). The outcome of this study suggests that the Pt species might have provided significant activation for the dehydrative cyclization. Accordingly, it became clear that $PtCl_4$ is involved in all the proposed catalytic cycles (Scheme 3.77).



Scheme 3.76 The plausible mechanism



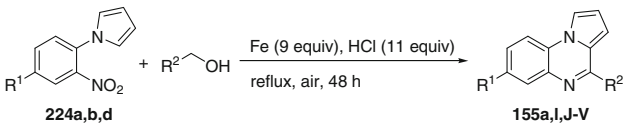
Scheme 3.77 Mechanistic studies (cycle D)

The first one-pot synthesis of 4-substituted pyrrolo[1,2-*a*]quinoxalines from 1-(2-nitrophenyl)pyrrole derivatives and various alcohols in redox conditions has been reported (Pereira and Thiéry 2012). As shown in Scheme 3.79, for all combinations of 1-(2-nitrophenyl)pyrrole derivatives and aliphatic or benzylic alcohols,

the desired 4-substituted pyrrolo[1,2-*a*]quinoxaline was observed as the only product. Most of the substrates examined provided good yields. The lowest yield was obtained when substituted 1-(2-nitrophenyl)pyrroles reacted with methanol as the substrate (R^2 = Me; R^1 = Cl, H, OMe) whereas ethanol was the best substrate for this reaction (R^2 = Et; R = Cl, H, OMe). The reactions with 1-(2-nitrophenyl) pyrroles bearing an electron-donating group such as a methoxy group meta to the nitro group decrease the product yields (R^1 = OMe; R^2 = Me, Et, *n*-Pr, *n*-Bu). Besides simple aliphatic alcohols, benzyl alcohol also reacted with the 1-(4-chloro-2-nitrophenyl)pyrrole to give the desired product in moderate yield (R^1 = Cl, R^2 = Bn). Furthermore, reactions between a secondary alcohol such as isopropanol and substituted 1-(2-nitrophenyl)pyrroles gave 4,5-dihydropyrrolo[1,2-*a*]quinoxaline derivatives (R^1 = Cl, R^2 = *i*-Pr; R^1 = H, R^2 = *i*-Pr). To further explore the scope of the reaction, all alcohols were also employed to react with 3-nitro-2-pyrrolopyridine. In general, good to moderate yields were obtained under standard reaction conditions (see Scheme 3.78).

The reaction to novel pyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazines **259** has been extended. Interestingly, the reaction of 3-nitro-2-pyrrolopyridine **258** with methanol and butyl alcohol resulted in a much lower yield (Scheme 3.79).

The most likely mechanism to rationalize this transformation is illustrated in Scheme 3.80. In an acidic medium, iron could catalyze the reduction of the nitrophenylpyrrole **224** to its amine counterpart **E** giving ferric salts (or ferrous salts) which in turn would be able to oxidize alcohols into aldehydes. Condensation of these latter with the amine **E** gives the iminium salts **F** which spontaneously cyclize leading to the dihydroquinoxalines **G** as previously described. Finally, a

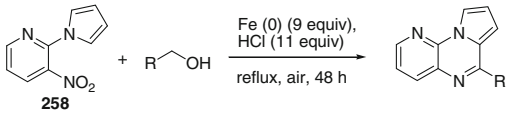


155 J-O R^1 = Cl
J R^2 = Et (80%)
K R^2 = Me (40%)
L R^2 = *n*-Pr (56%)
M R^2 = *i*-Pr (61%)
N R^2 = *n*-Bu (61%)
O R^2 = Bn (54%)

155 a,P-S R^1 = H
a R^2 = Me (31%)
P R^2 = Et (81%)
Q R^2 = *n*-Pr (56%)
R R^2 = *i*-Pr (60%)
S R^2 = *n*-Bu (50%)

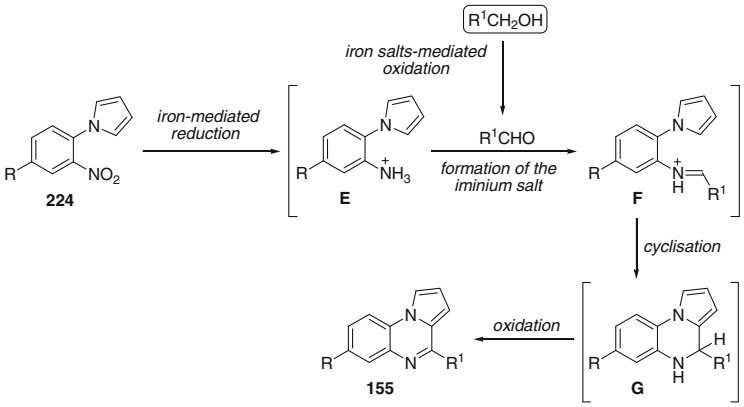
155 l,T-V R^1 = OMe
l R^2 = Me (20%)
T R^2 = Et (69%)
U R^2 = *n*-Pr (47%)
V R^2 = *i*-Pr (44%)

Scheme 3.78 Reactions of 1-(2-nitrophenyl)pyrrole derivatives with various alcohols



259 a R = Me (25%)
b R = Et (63%)
c R = Pr-*n* (50%)
d R = *i*-Pr (61%)
e R = *n*-Bu (33%)
f R = Bn (54%)

Scheme 3.79 Reactions of 3-nitro-2-pyrrolopyridine with various alcohols leading to pyrido[3,2-*e*]pyrrolo[1,2-*a*]pyrazines under optimal conditions



Scheme 3.80 Proposed mechanism

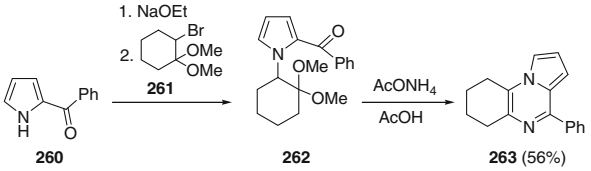
final oxidation produces the 4-alkyl or 4-phenylpyrroloquinoxalines **155** in moderate to good yield.

Thus, a rare one-pot reaction for assembling pyrrolo[1,2-*a*]quinoxalines from 1-(2-nitrophenyl)pyrroles and various alcohols. The nitro reduction, alcohol oxidation, heterocycle formation, and heterocycle oxidation were realized in a cascade. A wide range of these fused heterocycles bearing different alkyl and aryl groups in position 4 have been elaborated from suitable substrates; thereby 3-nitro-2-pyrrolopyridine was also compatible with this process, giving the corresponding fused tricyclic compounds.

3.2.7 Type PB2 Production Methods

During realization of the approach corresponding to the retrosynthetic path **PB2**, in contrast to all the above-mentioned methods for the synthesis of pyrrolo[1,2-*a*] quinoxalines where closure of the pyrazine ring takes place as a result of intramolecular cyclization, the concluding stage of the formation of the ring involves the participation of two reagents, i.e., it is intermolecular. The proposed method for the synthesis of pyrrolo[1,2-*a*]quinoxaline according to the **PB2** path involves alkylation of the sodium derivative of 2-benzoylpyrrole **260** by the dimethyl ketal of α-bromocyclohexanone **261** followed by treatment of the reaction product with ammonium acetate in acetic acid (Scheme 3.81). Here it should be noted that only one compound, 4-phenylpyrrolo[1,2-*a*]quinoxaline **263** was synthesized by this method (Shvedov et al. 1970).

Scheme 3.81 Synthesis and cyclisation of 1-(2,2-dimethoxycyclohexyl)-2-benzoylpyrrole

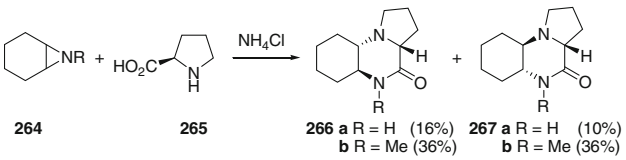


3.2.8 *Type PD Production Methods*

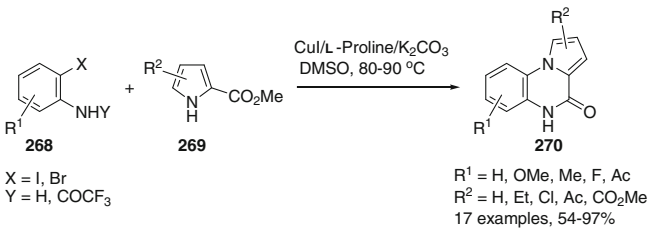
In reaction with derivatives of α-amino acids (glycine, L-alanine, L-phenylalanine, and L-proline) with opening of the aziridine ring and spontaneous closure of the piperazine ring condensed aziridines of type **264** lead to optically active representatives of new *trans*-bicycloperhydro-2(1*H*)-quinoxalines and tricycloperhydropyrrolo[1,2-*a*]quinoxalin-4(4*H*)-ones **266a**, **b** and **267a**, **b** (in the case of proline), the production of which represents realization of the retrosynthetic approach **PD** (Scheme 3.82) (Rees 1987).

In 2008, Yuan and Ma were proposed an effective one-pot method for the synthesis of pyrroloquinoxalines based on the condensation of *o*-aminoiodobenzene and its derivatives **268** with methoxycarbonylpyrroles **269** catalyzed by copper iodide and L-proline in the presence of potassium carbonate (Scheme 3.83) (Yuan and Ma 2008).

Promoted by CuI/2-hydroxybenzohydrazide catalytic system, a variety of pyrrolo[1,2-*a*]quinoxalines have been efficiently one-pot synthesized from pyrrole-2-carboxaldehyde and 2-haloanilines in moderate to excellent yields (Table 3.8) (Li et al. 2015).

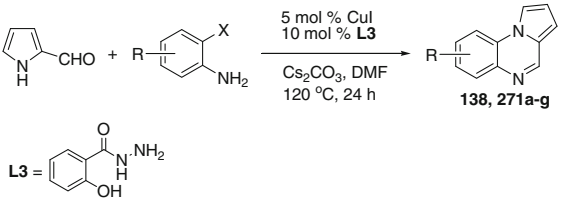


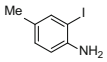
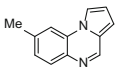
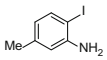
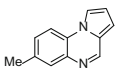
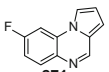
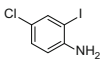
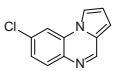
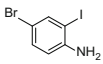
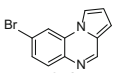
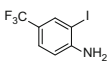
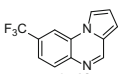
Scheme 3.82 Condensation of 7-R-7-azabicyclo[4.1.0]heptanes with α-amino acid derivatives



Scheme 3.83 Condensation of *o*-aminoiodobenzene and its derivatives with methoxycarbonylpyrroles

Table 3.8 CuI/**L3** catalyzed annulation of pyrrole-2-carboxaldehyde with substituted 2-haloaniline



Entry	2-Haloaniline	**138**, **271**	Yield (%)
1		 **138**	92
2		 **271a**	80
3		 **271b**	73
4		 **271c**	64
5		 **271d**	84
6		 **271e**	80
7		 **271f**	64
8		 **271g**	78
9		**138**	68
10		**138**	trace

As shown in Table 3.8, the cascade reactions were performed well enough for most of 2-iodoanilines with electronrich, electron-neutral, and electron-poor groups to afford corresponding pyrrolo[1,2-*a*]quinoxalines in good to excellent yields (entries 1–7). Moreover, heterocyclic aminoiodoarene could also react well enough with a 78 % yield (entry 8). Additionally, aminobromoarene provided a 68 % yield, while aminochloroarene afforded only a trace of the product under the experimental conditions (entries 9 and 10).

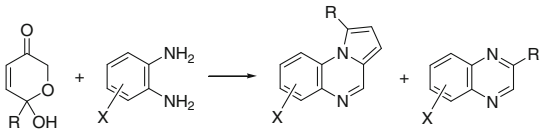
3.2.9 *Other Methods of Synthesis*

By such methods for the synthesis of pyrrolo[1,2-*a*]quinoxalines, we have in mind methods based either on condensed derivatives of pyrroles (a) either on compounds not containing a pyrrole ring or a quinoxaline system (b). During realization of approach (b), the pyrroloquinoxaline system can be produced through the initial formation of the quinoxaline system (b-*I*) or of the pyrrole ring (b-*II*). In this review, we only discuss the second version (b-*II*).

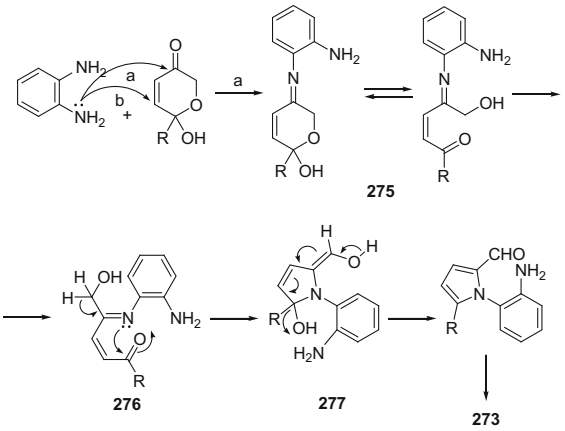
A typical example is the transformation of 4-(indolin-3-yl)pyrrolidinobenzimidazole **238** to the spiro derivative of pyrrolidinoquinoxaline **240** by the action of hydrochloric acid on the Stevens rearrangement, as shown above (Grantham and Meth-Cohn 1968).

Boiling of 6-hydroxy-6-(2,3,5-tri-**o**-benzoyl-β-**D**-ribofuranosyl)-2*H*-pyran-3-one **101** [obtained by the oxidation of 2-hydroxymethyl-5-(2,3,5-tri-**o**-benzoyl-β-**D**-ribofuranosyl)furan with *m*-chloroperbenzoic acid (Lefebvre 1972) or pyrazinium chlorochromate (Piancatelli et al. 1977)], and 1,2-DAB for 2 h in chloroform gives a 43 % yield of the quinoxaline derivative **274** and a 16 % yield of the pyrrolo[1,2-*a*]quinoxaline derivative **273** (Scheme 3.84); a plausible mechanism for the formation of the latter probably involves nucleophilic attack by the 1,2-DAB at the carbonyl group of the pyran ring in compound **272** followed by the formation of the Schiffs base **275**, which opens under the reaction conditions, giving the imino ketone **276**. Compound **276** undergoes cyclization to the enolic form **277** and is converted, after dehydration, into the tricycle **273** (path *a*) (Scheme 3.85). Compound **274** is probably formed by path b through addition of the 1,2-DABs to compound **272** in a reaction of the Michael type and ring opening, leading to the diketodiamine **278**. Compound **278** undergoes cyclization and gives the dihydroquinoxaline **279**, which forms compound **274** after the loss of dihydroxyacetone (Scheme 3.86) (Maeba et al. 1988).

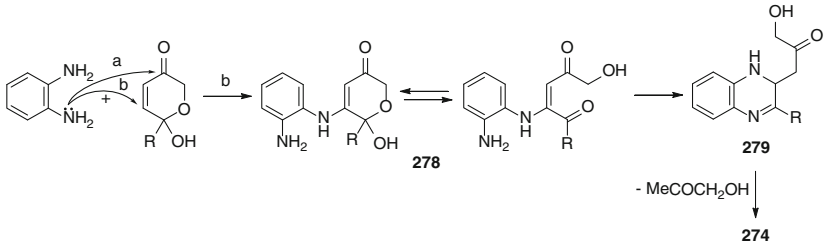
If derivatives of 1,2-DAB are used in this reaction, isomers differing in the substituents at positions 6 and 7 in the case of compounds of type **274** and at positions 7 and 8 in the case of compounds of type **273** are formed (Maeba et al. 1990).



Scheme 3.84 Condensation of 6-hydroxy-6-R-2*H*-pyran-3-one with 1,2-DABs



Scheme 3.85 Plausible mechanism for the formation of pyrrolo[1,2-*a*]quinoxalines

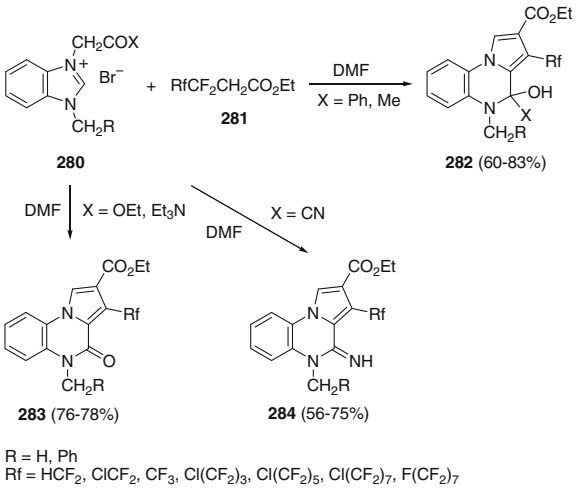


Scheme 3.86 Plausible mechanism for the formation of quinoxalines

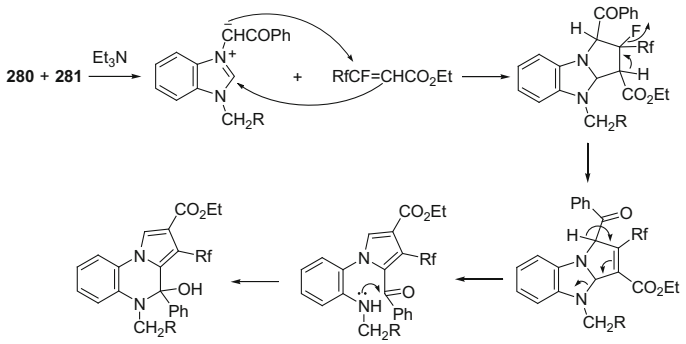
During the action of polyfluoroalkanoates **281** in the presence of bases the benzimidazole derivatives **280** rearrange, giving good yields of the 4-substituted pyrrolo[1,2-*a*]quinoxalines **282**–**284** (Scheme 3.87) (Zhang and Huang 1997, 1998).

In the opinion of the authors of (Zhang and Huang 1997, 1998), the pyrroloquinoxaline system is formed from the benzimidazole system according to the scheme presented below (Scheme 3.88).

The syntheses of isoindolo[2,1-*a*]quinoxalines and isoindolo[2,1-*a*]quinoxalin-6(5*H*)-ones have been achieved by either constructing the isoindole unit onto the quinoxaline core or vice versa. Although methods that exemplify either route have been reported (Dyker et al. 2000; Reeves et al. 2010), Potikha and coworkers (Sypchenko et al. 2012) suggested that the latter strategy of building the quinoxaline unit onto the isoindole structure offers better opportunities for functionalization. However, the methods to synthesize isoindolo[2,1-*a*]quinoxalines by Diana and coworkers (Diana et al. 2007, 2008; Girolamo and Patrizia 2008) and Potikha et al., which epitomize this strategy, involve the use of toxic or typical reagents such as KCN or *o*-(bromomethyl)benzophenone, respectively, and do not offer products in which the phenyl ring of the isoindole unit is substituted (Fig. 3.8).



Scheme 3.87 Synthesis of functionalized pyrrolo[1,2-*a*]quinoxalines based on benzimidazole derivatives



Scheme 3.88 Plausible mechanism for the synthesis of pyrrolo[1,2-*a*]quinoxalines

An operationally simple and efficient cascade strategy has been developed to access substituted isoindolo[2,1-*a*]quinoxalines through a one-step copper-catalyzed C–N coupling reaction between substituted 2*H*-isoindole-1-carbaldehydes and substituted 2-halophenylamines (Biswas and Batra 2013).

In the first phase, substituted 2*H*-isoindole-1-carbaldehydes **285a–e** were treated with 2-iodoaniline **286a** in the presence of CuI under the standardized conditions. All reactions afforded the corresponding products **287a**–e in excellent yields (Table 3.9, entries 1–5). The electronic nature of the substituents present on the

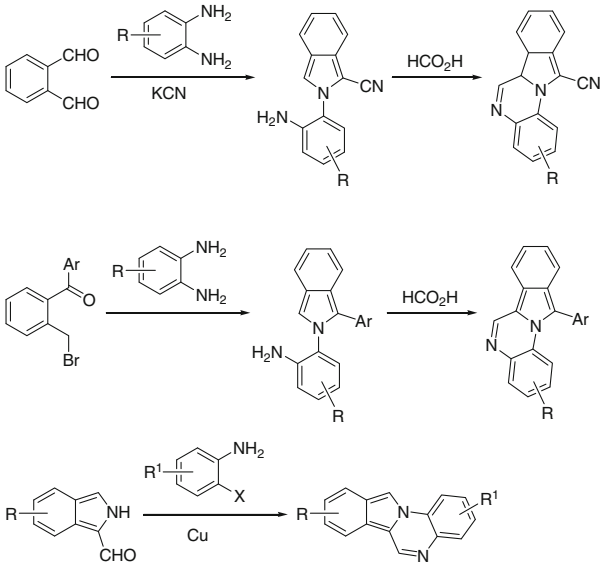
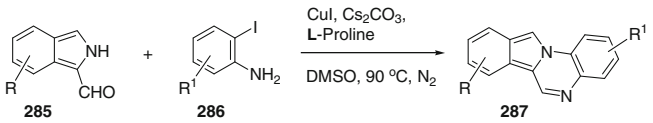


Fig. 3.8 Different protocols for the syntheses of substituted isoindolo[2,1-*a*]quinoxalines

phenyl ring of the isoindole unit did not influence the formation of products (Table 3.9, entries 2–5). Subsequently, the reaction of 2*H*-isoindole-1-carbaldehyde **285a** was investigated with the various substituted 2-iodoanilines **286b–f**. Although the anilines that contained methyl groups (i.e., **286b** and **286f**) gave products **287f** and **287o**, respectively, in good yields (Table 3.9, entries 6 and 10), the 2-iodoanilines that contained electron-withdrawing substituents such as fluoro or trifluoromethyl produced the respective products **287k** and **287m** only in moderate yields (Table 3.8, entries 7 and 8). In contrast, aniline **286e** with the nitro group failed to furnish the desired product **287n** (Table 3.9, entry 9), and this reaction led to an inseparable mixture of products after 6 h of reaction time. To further investigate the generality of the protocol, substituted 2*H*-isoindole-1-carbaldehydes **285b** and **285c** were treated with substituted 2-iodoanilines **286b** and **286c** to furnish the products **287g**, **287h**, and **287l** (Table 3.9, entries 11–13). As before, the reaction of 4-fluoro-2-iodoaniline gave product **287l** in relatively lower yields (Table 3.9, entry 13).

Unlike the reaction with 2-iodoaniline that was completed in 8 h, the reaction with 2-bromoaniline (in the presence of CuI, base, and L-proline in DMSO) took 16 h to reach completion and produce the product in a 78 % yield (Table 3.10,

Table 3.9 Scope of reaction with different 2*H*-isoindole-1-carbaldehydes and 2-iodoanilines



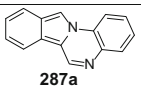
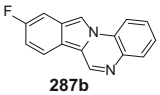
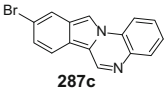
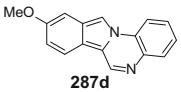
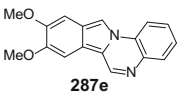
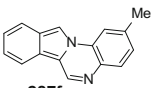
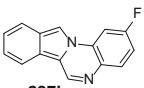
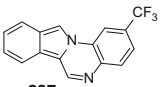
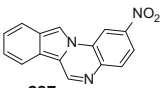
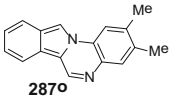
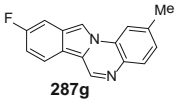
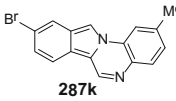
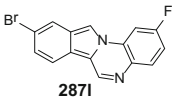
Entry	285	R	286	R^1	287	Yield (%)
1	**285a**	H	**286a**	H	 **287a**	82
2	**285b**	F-5	**286a**	H	 **287b**	79
3	**285c**	Br-5	**286a**	H	 **287c**	76
4	**285d**	MeO-5	**286a**	H	 **287d**	75
5	**285e**	$(MeO)_2$-4,5	**286a**	H	 **287e**	74
6	**285a**	H	**286b**	Me-4	 **287f**	78
7	**285a**	H	**286c**	F-4	 **287k**	52
8	**285a**	H	**286d**	CF_3-4	 **287m**	61
9	**285a**	H	**286e**	NO_2-4	 **287n**	not observed

Table 3.9 (continued)

10	**285a**	H	**286f**	Me_2-4,5	 **287o**	75
11	**285b**	F-5	**286b**	Me-4	 **287g**	82
12	**285c**	Br-5	**286b**	Me-4	 **287k**	79
13	**285c**	Br-5	**286c**	F-4	 **287l**	47

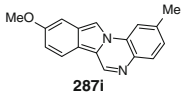
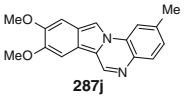
entry 1). Nevertheless, the success of the strategy was investigated by employing different 2*H*-isoindole-1-carbaldehydes (i.e., **285a–e**) and varying the 2-bromoanilines (i.e., **288a–c**). It should be pointed out that unlike the reactions of 2-iodoanilines, those with 2-bromoanilines took a longer time to reach completion, but the isolated yields were marginally better (Table 3.10).

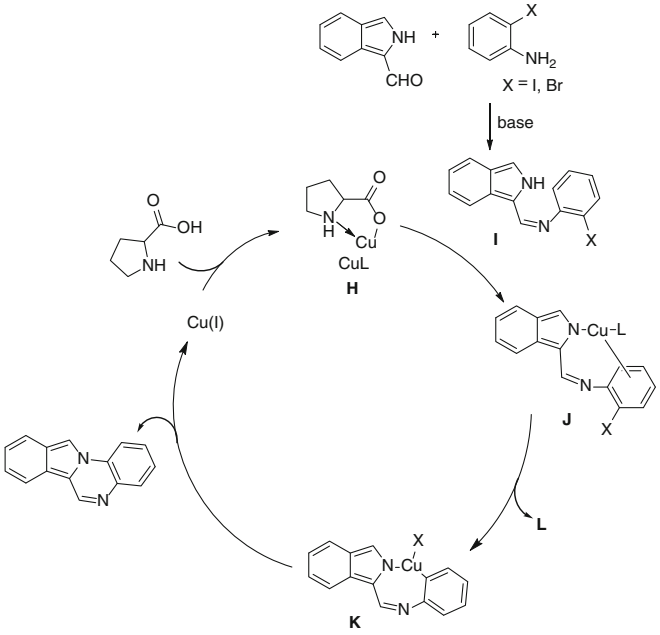
A plausible mechanism for the formation of isoindolo[2,1-*a*]quinoxaline is delineated in Scheme 3.89. Initially, CuL complex **H** undergoes a reaction with aldimine **I** to afford intermediate **J**. The loss of the ligand (**L**) leads to the copper complex **K** that undergoes a reductive elimination to afford the product.

Another straightforward procedure is described to prepare substituted isoindolo [2,1-*a*]quinoxalin-6(5*H*)-ones, which involved the transformation of a substituted 2*H*-isoindole-1-carboxylic acid into an acid chloride (Scheme 3.90) followed by a coupling reaction with a substituted 2-iodophenylamine and a copper-catalyzed C–N coupling reaction (Table 3.11).

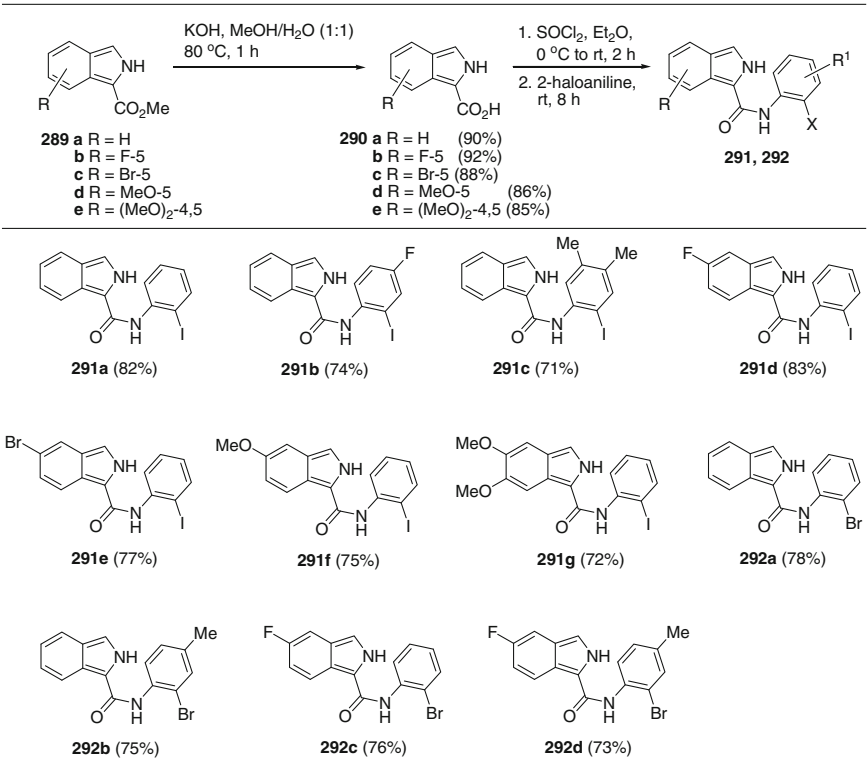
As already discussed above, the substituted amides of pyrrolecarboxylic acids **185** undergo cyclization with sodium hydride to substituted pyrroloquinoxaline-4-ones **186** (Rotas et al. 2004). However, together with the usual *ipso* substitution of the nitro group, leading to the formation of pyrroloquinoxalines **297**, the anion **295** undergoes a Smiles rearrangement to the anion **296**, the further cyclization of which leads to the formation of the pyrroloquinoxaline **298** (Scheme 3.91) (Rotas et al. 2004).

Table 3.10 Scope of reaction with different 2*H*-isoindole-1-carbaldehydes and 2-bromoanilines

Entry	285	R	288	R^1	287	Yield (%)
1	**285a**	H	**288a**	H	**287a**	78
2	**285b**	F-5	**288a**	H	**287b**	75
3	**285c**	Br-5	**288a**	H	**287c**	79
4	**285d**	MeO-5	**288a**	H	**287d**	80
5	**285e**	$(MeO)_2$-4,5	**288a**	H	**287e**	82
6	**285a**	H	**288b**	Me-4	**287f**	86
7	**285b**	F-5	**288b**	Me-4	**287g**	84
8	**285c**	Br-5	**288b**	Me-4	**287h**	81
9	**285d**	MeO-5	**288b**	Me-4	 **287i**	78
10	**285e**	$(MeO)_2$-4,5	**288b**	Me-4	 **287j**	77
11	**285a**	H	**288c**	F-4	**287k**	72
12	**285c**	Br-5	**288c**	F-4	**287l**	73



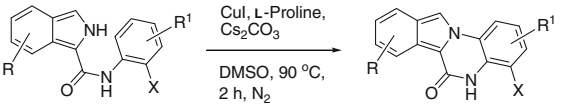
Scheme 3.89 A plausible mechanism for the synthesis of isoindolo[2,1-*a*]quinoxaline



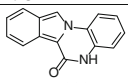
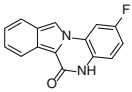
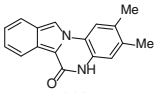
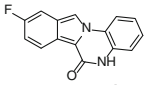
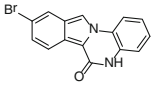
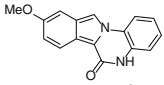
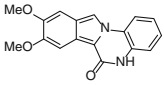
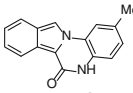
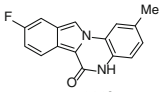
Scheme 3.90 Synthesis of isoindolecarboxamides

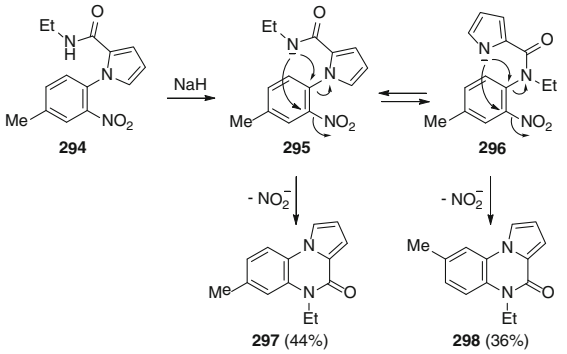
If there is an *o*-fluorine-substituted phenyl group in the amide fragment, attack by the rearranged anion **301** leads both to cyclization with substitution of the nitro group in one of the aryl fragments and the formation of the pyrroloquinoxaline **302** and to substitution of the fluorine atom in other aryl group and the formation of pyrroloquinoxaline **303** (Scheme 3.92) (Rotas et al. 2004).

Table 3.11 Scope of intramolecular coupling reaction of different 2*H*-isoindole-1-carboxamides

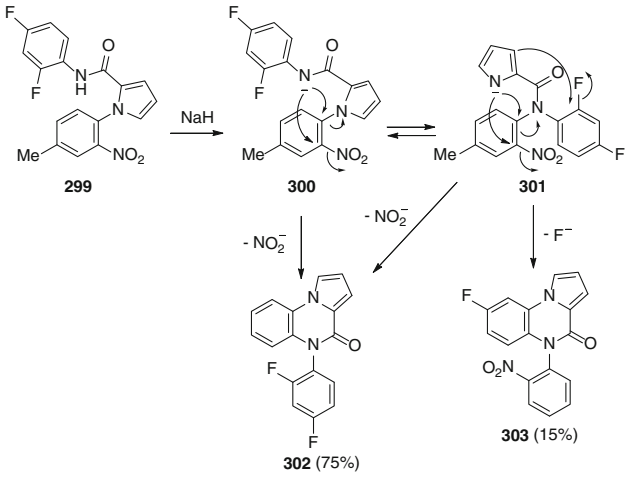


291 or 292 **293**

Entry	291/292	293	Yield (%)
1	**291a**	 **293a**	78
2	**291b**	 **293b**	76
3	**291c**	 **293c**	80
4	**291d**	 **293d**	81
5	**291e**	 **293e**	75
6	**291f**	 **293f**	71
7	**291g**	 **293g**	72
8	**292a**	**293a**	75
9	**292c**	**293d**	68
10	**292b**	 **293h**	82
11	**292d**	 **293i**	73



Scheme 3.91 Plausible mechanisms for the synthesis of pyrrolo[1,2-*a*]quinoxalines from *N*-ethyl-1-(4-methyl-2-nitrophenyl)-1*H*-pyrrole-2-carboxamide when exposed to sodium hydride



Scheme 3.92 Plausible mechanisms for the synthesis of pyrrolo[1,2-*a*]quinoxalines from *N*-(2,4-difluorophenyl)-1-(4-methyl-2-nitrophenyl)-1*H*-pyrrole-2-carboxamide when exposed to sodium hydride

Table 3.12 Probable and implemented methods for the synthesis of pyrrolo[1,2-*a*] quinoxalines based on phenylpyrrole derivatives

Based on phenylpyrrole derivatives	
Possible	Implemented (number of papers)
A1, **A2**, **A3**, **A4**	**A1** (12), **A2** (8), **A3** (2), **A4** (1)
B1, **B2**	**B1** (34), **B2** (2)
C1, **C2**	**C1** (0), **C2** (0)
D	**D** (2)
E	**E** (0)
Other methods	(4)

3.2.10 Conclusion

According to the data in the Table 3.12, of the ten possible methods for the synthesis of pyrrolo[1,2-*a*]quinoxalines, the most successful are the methods based on the **PA1** and **PB1** approaches, while as shown above the methods based on the **PC1**, **PC2**, and **PE** approaches can only be realized when effective methods have been developed for the C–N coupling of benzene derivatives, amines, and pyrroles, making it possible to synthesize the required structural units for the production of pyrrolo[1,2-*a*]quinoxalines depending on the required objective.

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Chapter 4
Synthesis of Imidazo[1,5-*a*]- and Imidazo[1,2-*a*]quinoxalines

4.1 Introduction

Heterocyclic systems containing the quinoxaline moiety are widely used in practice. Many of them have high biological activity (for example, antitumour (Baffert et al. 2010; Lee et al. 2010), antiviral (El-Ashry et al. 1999), antibacterial (Seitz et al. 2002; Badran et al. 2003), antiinflammatory (Abu-Hashem et al. 2010)) or are inhibitors of kinases, enzymes that catalyze phosphate group transfer from ATP (Frohlich et al. 1999; Srinivas et al. 2007; Khattab et al. 2010). Quinoxalines are used as antibiotics (Myers et al. 2003; Dietrich and Diederchsen 2005), dyes (Brock et al. 1999), electroluminescent materials (Duan et al. 2003; Schneidenbach et al. 2010), organic semiconductors (Dailey et al. 2001), DNA-binding agents (Sasmal et al. 2010), as well as 'building blocks' in synthesis of anion (Sessler et al. 2002a) and cavitand (Sessler et al. 2002b; Castro et al. 2004) receptors, corrosion inhibitors (Zarrouk et al. 2010), etc. Among the derivatives annulated at bond *a* of the quinoxaline ring, imidazoquinoxalines hold a special place, since many pharmaceuticals based on them have been developed. In particular, drugs U-80447 and U-97775, which have a sedative effect, are imidazo[1,5-*a*]quinoxaline derivatives, and antiallergic drug Dazoquinast and compound LU-73068, an anticonvulsant and glycine antagonist, are imidazo[1,2-*a*]quinoxaline derivatives (Fig. 4.1) (Negwer and Scharnow 2001).

In the last years, interest in imidazoquinoxalines continues unabated due to the search for compounds with antitumour activity (Nadler et al. 2002; Morjaria et al. 2006; Moarbess et al. 2008a; Deleuze-Masquéfa et al. 2009a, b; Khier et al. 2009, 2010a), which selectively act on the central nervous system (Malamas et al. 2010, 2011a) and inhibit poly(ADP-ribose) polymerase (Giranda et al. 2008). This circumstance attracts the attention of organic chemists to the development of new methods of synthesis of different imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxalines. However, currently, information on the synthesis of such compounds remains fragmentary. In monograph (Cheeseman and Cookson 1979), data on different

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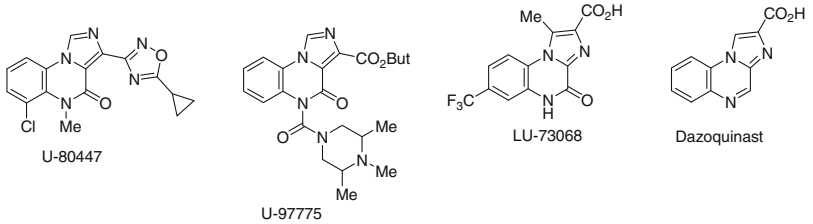
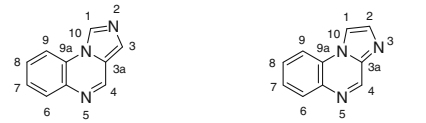


Fig. 4.1 Imidazoquinoxaline-based drugs

Fig. 4.2 Imidazoquinoxaline structures



imidazoquinoxaline systems have been reported, mainly covering the period from 1965 to 1975, although the first publication (King and Clark-Lewis 1951) on the synthesis of imidazo[1,5-*a*]quinoxalines appeared in 1951 and that on the synthesis of imidazo[1,2-*a*]quinoxalines, in 1962 (Heine and Brooker 1962). In review (Horton et al. 2003) dealing with the combinatorial synthesis of the most important bicyclic structures, selected methods of synthesis of about 20 fused heterocycles, including imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxalines, have been considered. The authors present available data without their comparative analysis.

In the present chapter, we consider all possible variants of assembly of imidazo [1,5-*a*]- and imidazo[1,2-*a*]quinoxaline skeletons from various fragments (Fig. 4.2).

The principle of systematization of data is the same as used in our previous reviews (Kalinin and Mamedov 2010; Mamedov and Kalinin 2010) focusing on pyrrolo[1,2-*a*]quinoxalines. Formation of the structure of each heterocyclic system is considered without including the benzene ring. The corresponding figures show all possible assembly variants in which quinoxaline or imidazole derivatives act as the initial compounds.

4.2 Synthesis of Imidazo[1,5-*a*]quinoxalines on the Basis of Quinoxaline Derivatives

As shown by analysis of the structures (Fig. 4.3), the imidazo[1,5-*a*]quinoxaline system can be formed from quinoxaline derivatives (labeled with the subscript **Q**) in the following ways:

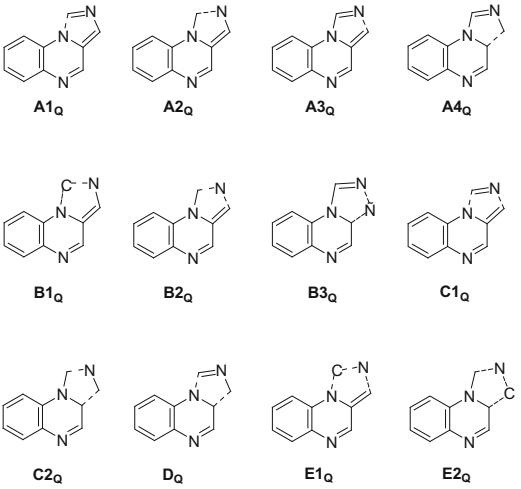


Fig. 4.3 Possible variants of construction of the imidazo [1,5-*a*]quinoxaline system on the basis of quinoxaline derivatives (the forming bonds are shown by the *dashed lines*)

- through intramolecular cyclization with formation of the N(10)–C(1), C(1)–N (2), N(2)–C(3) or C(3)–C(3a) bonds (variants **A1$_Q$**–**A4$_Q$**);
- through different intermolecular condensations of quinoxaline derivatives
  - (a) with equivalents of monoatomic carbon synthons accompanied by the formation of the N(10)–C(1) and C(1)–N(2) or N(2)–C(3) and C(3)–C(3a) bonds (variants **B1$_Q$** and **B3$_Q$**),
  - (b) with equivalents of monoatomic nitrogen-containing synthons accompanied by the formation of the C(1)–N(2) and N(2)–C(3) bonds (variant **B2$_Q$**),
  - (c) with diatomic molecules accompanied by the formation of the C(1)–N(2) and C(3)–C(3a) or N(10)–C(1) and N(2)–C(3) bonds (variants **C2$_Q$** and **C1$_Q$**),
  - (d) with triatomic molecules accompanied by the formation of the N(10)–C(1) and C(3)–C(3a) bonds (variant **D$_Q$**);
- through the three-component reaction leading to the formation of the N(10)–C (1), C(1)–N(2) and N(2)–C(3) or C(1)–N(2), N(2)–C(3), and C(3)–C(3a) bonds (variants **E1$_Q$** and **E2$_Q$**).

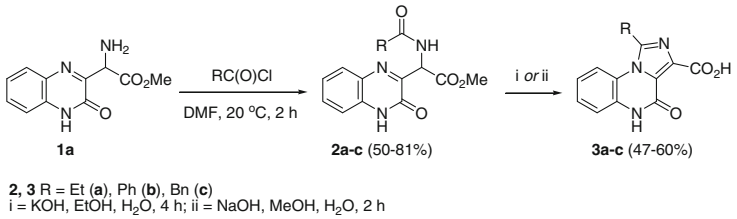
4.2.1 Methods of Formation of the N(10)–C(1) Bond (Variant A1$_Q$)

Imidazole ring annulation according to variant **A1$_Q$** can be a result of the nucleophilic attack of the nitrogen atom in the 1- or 4-position of quinoxaline at the electrophilic carbon atom of the C–N–C moiety of the substituent at the C(2) or C(3) atom. Such substituents are acylaminomethyl, isocyanatomethyl, benzylaminomethyl, etc.

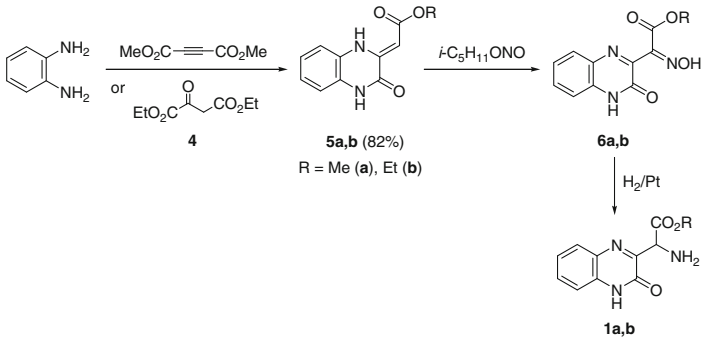
groups. As a rule, the methods of synthesis corresponding to this variant are rather simple from the preparative point of view, and the reactions proceed in high yields. The starting reactants can be, for example, methyl 2-amino-2-[quinoxalin-2(1*H*)-one **1a** (Scheme 4.1) (Danswan et al. 1982; Ager et al. 1988). In particular, their reaction with carboxyl chlorides yields acylated derivatives **2**; when heated for a while in alcohol solutions in the presence of potassium hydroxide, the latter undergo intramolecular cyclization to give imidazo[1,5-*a*]quinoxalines **3**. The major disadvantage of this method is that the corresponding starting compounds are obtained by multistage reactions.

Two procedures of synthesis of aminomethylquinoxalines **1** have been developed. One of them involves three stages: (a) condensation of ethyl ethoxalylacetate **4** or dimethyl acetylenedicarboxylate with 1,2-DAB to give quinoxalines **5**, (b) the reaction of the latter with isopentyl nitrite, and (c) reduction of resulting oximes **6** (Scheme 4.2) (Danswan et al. 1982; Ager et al. 1988).

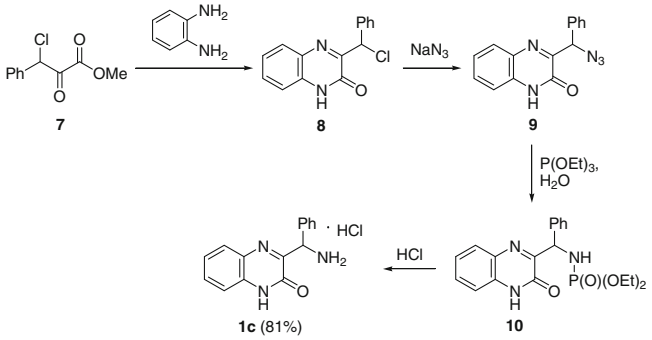
The other procedure comprising four stages involves the following reactions: (a) condensation of methyl chlorophenylpyruvate **7**, synthesized by the Darzan reaction from methyl dichloroacetate and benzaldehyde (Mamedov and Nuretdinov 1992), with 1,2-DAB to give 3-(α-chlorobenzyl)quinoxalin-2(1*H*)-one **8** (Mamedov et al. 1990); (b) the reaction with sodium azide to give corresponding azide **9**;



Scheme 4.1 Synthesis of imidazo[1,5-*a*]quinoxalines from acylated derivatives of methyl 2-amino-2-[quinoxalin-2(1*H*)-onylidene]acetate



Scheme 4.2 Synthesis of aminomethylquinoxalines



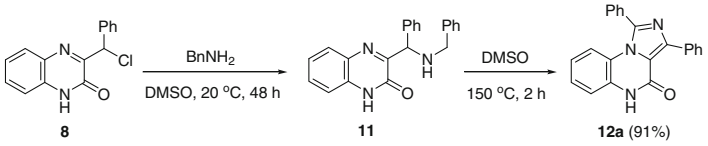
Scheme 4.3 Synthesis of 3-(α-chlorobenzyl)quinoxalin-2(1*H*)-one

(c) Staudinger reaction with triethyl phosphate yielding phosphoramidate **10** and (d) the reaction of the latter with dry HCl, which leads to target amine **1c** in the form of hydrochloride (Scheme 4.3) (Mamedov et al. 2003).

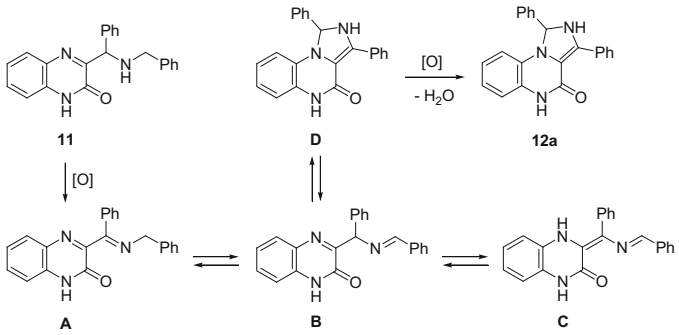
When heated for 2 h or thermolyzed for 10 min at 225 ± 3 °C, 3-(α-benzylaminobenzyl)quinoxalin-2(1*H*)-one **11**, synthesized by the reaction of 3-(α-chlorobenzyl)quinoxalin-2(1*H*)-one **8,** and benzylamine in DMSO at room temperature, undergoes intramolecular cyclocondensation to give imidazoquinoxaline **12a** (Scheme 4.4) (Mamedov et al. 2004).

Annulation of the imidazole ring to compound **11** evidently occurs through the oxidation of the latter to imine **A** which can also exist as tautomers **B** and **C**. The nucleophilic attack of the N(4) atom at the carbon atom of the imine moiety in structure **B** leads to the closure of the imidazole ring to form dihydroimidazoquinoxaline system **D**, and further oxidation of the latter under the reaction conditions leads to tricyclic compound **12a**. Air oxygen or a solvent (dimethyl sulfoxide) can act as an oxidant in this case (Scheme 4.5).

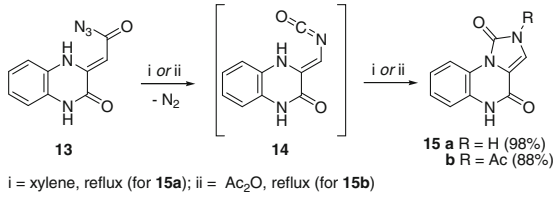
Heating 3-(azidocarbonylmethylene)-1,2,3,4-tetrahydroquinoxalin-2-one **13**, synthesized from the corresponding hydrazide, in xylene or acetic anhydride first presumably induces the Curtius rearrangement to give isocyanate **14**, and the closure of the imidazole ring in it leads to imidazo[1,5-*a*]quinoxalinediones **15** in high yields (Kurasawa et al. 1983). The reaction in xylene yields imidazoquinoxalinedione **15a** with unsubstituted imidazole nitrogen atom, and the reaction in acetic anhydride affords its acetylated derivative **15b** (Scheme 4.6).



Scheme 4.4 Thermolysis of 3-(α-benzylaminobenzyl)quinoxalin-2(1*H*)-one



Scheme 4.5 Oxidative cyclization of 3-(α-benzylaminobenzyl)quinoxalin-2(1*H*)-one

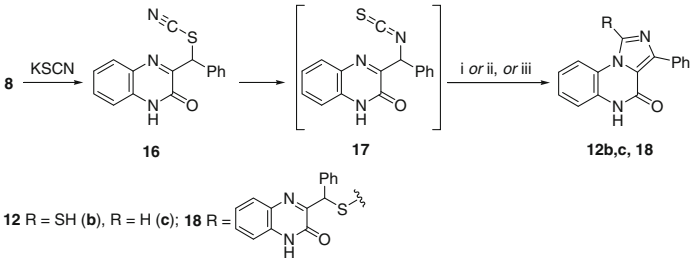


Scheme 4.6 Synthesis of imidazo[1,5-*a*]quinoxalinediones from 3-(azidocarbonylmethylene)-1,2,3,4-tetrahydroquinoxalin-2-ones

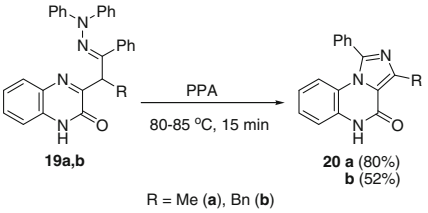
Quinoxaline-containing thiocyanate **16**, which forms in the reaction of 3-(α-chlorobenzyl)quinoxalinone **8** with potassium thiocyanate, isomerizes into the S-analog of isocyanate **14**–isothiocyanate **17**. The latter acts as a starting compound for the synthesis of imidazo[1,5-*a*]quinoxalines **12b**, **c** and **18** through intramolecular cyclization. The direction of the process depends on the reaction conditions (temperature, pH of a medium, solvent). Thermolysis of compound **16** in the absence of the solvent leads to 1-sulfanylimidazoquinoxaline **12b**, isomeric to compounds **16** and **17**, in quantitative yield. Heating thiocyanate **16** in the presence of Et_3N in DMF gives compound **18** in 60 % yield, while heating in DMSO leads to imidazo[1,5-*a*]quinoxaline **12c** (yield 11 %) in a mixture with other products (Scheme 4.7) (Mamedov et al. 2002b).

Under the action of polyphosphoric acid (PPA), hydrazones **19a**, **b** lose diphenylamine and convert into imidazo[1,5-*a*]quinoxalines **20a**, **b** (Scheme 4.8) (Kollenz 1972).

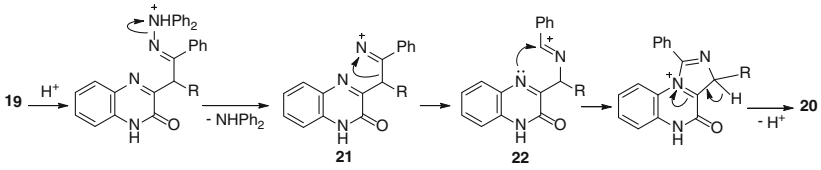
The authors believe that compounds **20** form as a result of generation of nitrenium ion **21** after diphenylamine elimination [just as it happens in the Schmidt reaction (Sahasrabudhe et al. 2003; Katori et al. 2010)], migration of the alkyl group to the nitrogen atom and closure of the imidazole ring in carbocation **22** (Scheme 4.9).



Scheme 4.7 Synthesis of imidazo[1,5-*a*]quinoxalines from the reaction of 3-(α-chlorobenzyl) quinoxalinone with potassium thiocyanate



Scheme 4.8 Synthesis of imidazo[1,5-*a*]quinoxalines from (*Z*)-3-(1-(2,2-diphenylhydrazono)-1-phenylpropan-2-yl and 1,3-diphenylpropan-2-yl)quinoxalin-2(1*H*)-ones

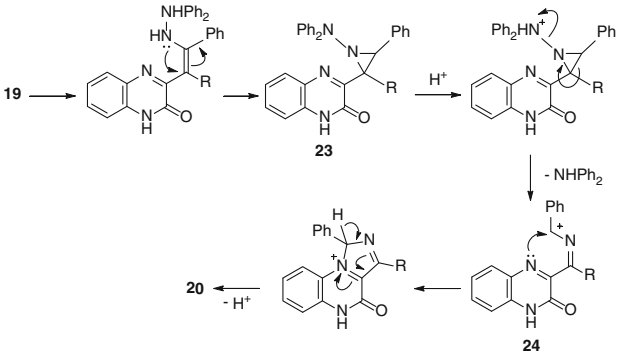


Scheme 4.9 Plausible mechanism for the formation of imidazo[1,5-*a*]quinoxalines from hydrazones

Another way can be suggested through the intermediate formation of aziridine derivative **23** and the acid-catalyzed opening of the aziridine ring at the C(2)–C(3) bond with removal of diphenylamine and formation of carbocation **24** (Scheme 4.10).

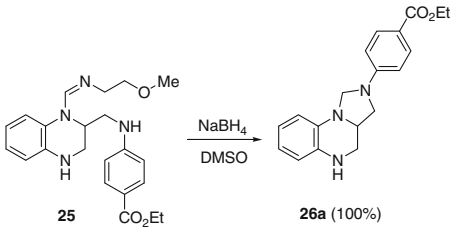
4.2.2 Method of Formation of the C(1)–N(2) Bond (Variant A2$_Q$)

Intramolecular cyclization involving the amine nitrogen atom of the substituent in the 2-position and the carbon atom of the imine moiety of the substituent in the



Scheme 4.10 Alternatime mechanism for the formation of imidazo[1,5-*a*]quinoxalines from hydrazones via aziridine derivatives

Scheme 4.11 Intramolecular cyclization involving the amine nitrogen atom of the substituent in the 2-position of tetrahydroquinoxaline derivative



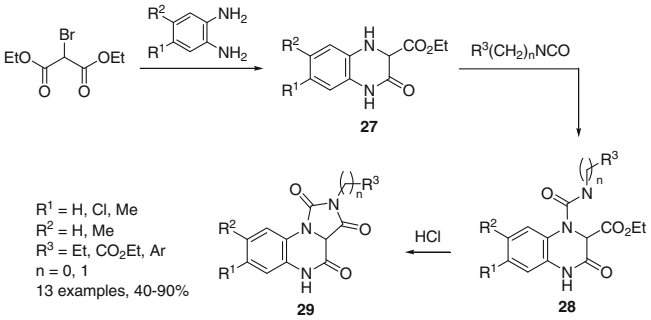
1-position in tetrahydroquinoxaline **25** leads to hydrogenated imidazo[1,5-*a*] quinoxaline **26a** in quantitative yield (Scheme 4.11) (Benkovic et al. 1973).

4.2.3 *Method of Formation of the N(2)–C(3) Bond (Variant A3$_Q$)*

The reaction of diethyl bromomalonate and 1,2-DABs gives tetrahydroquinoxalin-2-ones **27**, which are then introduced into the aminoacylation reaction (Ahmad et al. 1964). On heating in 2 M HCl, carbamoyl derivatives **28** undergo intramolecular amidation to give imidazo[1,5-*a*]quinoxaline-1,3,4(2*H*,3*H*,5*H*)-triones **29** (Scheme 4.12) (Varano et al. 2001).

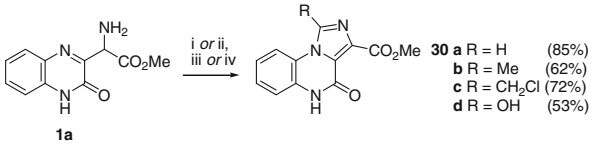
4.2.4 *Methods of Formation of the N(10)–C(1) and C(1)–N(2) Bonds (Variant B1$_Q$)*

Only one of the three possible variants of formation of the imidazo[1,5-*a*]quinoxaline system on the basis of reactions of quinoxaline and equivalents of monoatomic



Scheme 4.12 Synthesis imidazo[1,5-*a*]quinoxaline-1,3,4(2*H*,3*H*,5*H*)-triones

Scheme 4.13 Cyclization of methyl 2-amino-2-(quinoxalin-2(1*H*)-on-3-yl) acetate when exposed to one carbon suppliers



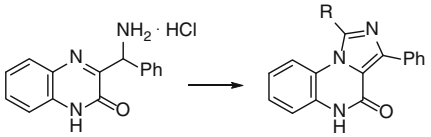
i = $HC(OEt)_3$, *p*-TsOH, reflux, 2-3 h; ii = $MeC(OEt)_3$, *p*-TsOH, reflux, 2-3 h
iii = $ClCH_2C(OEt)_3$, *p*-TsOH, reflux, 2-3 h; iv = Im_2CO, KOH, MeOH

synthons (see Fig. 4.3) is known. This variant corresponds to the formation of the bond of the C(1) carbon atom with two nitrogen atoms in the 2- and 10-positions. In particular, the condensation of 3-aminomethylquinoxalin-2(1*H*)-one **1a** with triethyl orthoformate or triethyl orthoacetate in the presence of *p*-toluenesulfonic acid (*p*-TsOH) upon heating under reflux for 2–3 h leads to imidazoquinoxalines **30a–c** (Scheme 4.13) (Malamas et al. 2010, 2011a). 1-Hydroxy derivative of imidazoquinoxaline **30d** is synthesized from amine **1a** by the reaction with 1,1′-carbonyldiimidazole (Im_2CO) in methanol in the presence of KOH (Danswan et al. 1982).

The reaction of 3-(α-aminobenzyl)quinoxalin-2(1*H*)-one hydrochloride **1c** with triethyl orthoformate does not require additional acid catalysis. The reaction lasts for 6 h to yield imidazoquinoxaline **12c** (Mamedov et al. 2003). Refluxing of compound **1c** with acetic anhydride for 4 h leads to 1-methylimidazoquinoxalin-4-one **12d** (Mamedov et al. 2003). Aromatic aldehydes can also be used as the equivalents of monoatomic synthons. As distinct from the above reactions, the reaction of compound **1c** with aromatic aldehydes requires longer time. In particular, the reaction of 4-methoxyethoxybenzaldehyde with quinoxaline **1c** in boiling dioxane lasts for 15 h to give *p*-methoxyphenylimidazoquinoxalin-4-one **12e** in high yield.

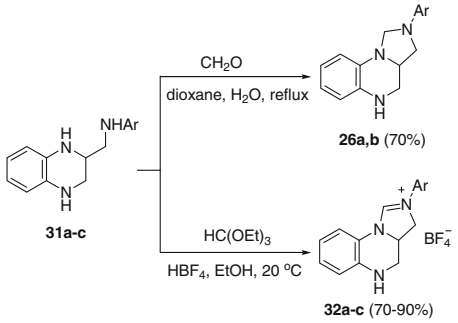
Decreasing the reaction duration to 9 h in the case of benzaldehyde gives 1-phenylimidazoquinoxaline **12a** in only 58 % yield. Amine hydrochloride **1c** reacts with carbon disulfide in methanol in the presence of KOH to give 1-sulfanylimidazoquinoxaline **12b** (Table 4.1) (Mamedov et al. 2003).

Table 4.1 Cyclization of 3-(α-aminobenzyl)quinoxalin-2(1*H*)-one hydrochloride when exposed to one carbon suppliers



1c **12a-e**

12	R	Reagent	Conditions	Yield (%)
12a	Ph	PhCHO	dioxane, reflux, 9 h	58
12b	SH	CS_2	KOH, MeOH	90
12c	H	$HC(OEt)_3$	6 h	84
12d	Me	Ac_2O	reflux, 4 h	53
12e	C_6H_4OMe-4	$HOCC_6H_4OMe$-4	dioxane, reflux,15h	93

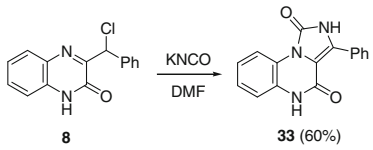


Scheme 4.14 Cyclization of arylaminomethyltetrahydroquinoxalines when exposed to one carbon suppliers

The reaction of arylaminomethyltetrahydroquinoxalines **31a–c** with formaldehyde leads to hexahydroimidazoquinoxalines **26a**, **b** and the reaction with triethyl orthoformate in the presence of tetrafluoroboric acid gives imidazolium salts **32a–c** (Scheme 4.14) (Benkovic et al. 1969, 1972).

4.2.5 Methods of Formation of the N(10)–C(1) and N(2)–C(3) Bonds (Variant $C1_Q$)

There are two possible ways of designing imidazo[1,5-*a*]quinoxalines according to variants **C**: the introduction of the C(1)–N(2) or N(2)–C(3) fragment into quinoxaline derivatives. However, only the first one (variant $\mathbf{C1_Q}$) has been described in the



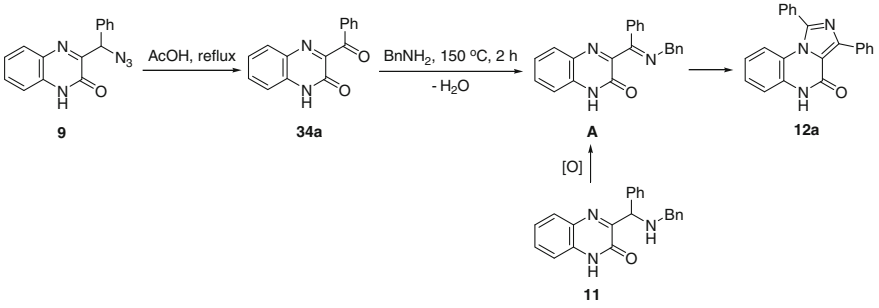
Scheme 4.15 Reaction of 3-(α-chlorobenzyl)quinoxalin-2(1*H*)-one with potassium isothiocyanate

literature. Evidently, this is due to the ease of synthesis of appropriate starting quinoxalines (Mamedov et al. 1990; Mamedov and Nuretdinov 1992). In particular, the reaction of 3-(α-chlorobenzyl)quinoxalin-2(1*H*)-one **8** with potassium isocyanate in boiling DMF for 6 h leads to 3-phenylimidazoquinoxaline-1,4-dione **33** (Scheme 4.15) (Mamedov et al. 2003).

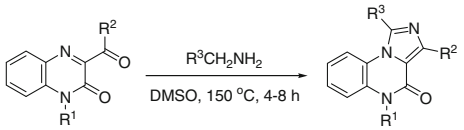
The reaction of heterocyclic ketone **34a** with benzylamine on heating in DMSO affords imidazoquinoxaline **12a** in quantitative yield. This result is yet another evidence that the formation of imidazoquinoxaline **12a** in the reaction of 3-(α-chlorobenzyl)quinoxalin-2(1*H*)-one **8** with benzylamine in DMSO also occurs through amine **11** and intermediate imine **A** (see Scheme 4.5) (Mamedov et al. 2004). 3-Benzoylquinoxalin-2(1*H*)-one **34a** readily forms upon thermolysis of azide **9** in boiling acetic acid (Scheme 4.16) (Mamedov et al. 2002a).

Analogously, *N*-alkylated derivatives **34c–h** and 3-acetylquinoxalin-2-one **34b** [instead of 3-benzoylquinoxalin-2-one **34a**] react with 3-aminomethylpyridine (β-picolylamine) (instead of benzylamine) to give imidazo[1,5-*a*]quinoxalin-4-ones **35a–l** (Scheme 4.17) (Kalinin and Mamedov 2008a; Mamedov et al. 2009; Kalinin et al. 2013).

In addition, compounds containing two benzoylquinoxaline moieties were introduced into this reaction. This enabled the synthesis of bis(imidazoquinoxaline)s in which the quinoxaline moieties are linked with each other through various spacers. In particular, the reaction of α,ω-bis(3-benzoylquinoxalin-2-on-1-yl) derivatives **36** with benzyl- and picolylamines on heating in DMSO yields α,ω-bis(1,3-diphenyl- and 1-pyridyl-3-phenyl-imidazo[1,5-*a*]quinoxalin-4-on-5-yl) derivatives **37a–g**



Scheme 4.16 Oxidative imidazoannulation of 3-benzoylquinoxalin-2-one with benzylamine

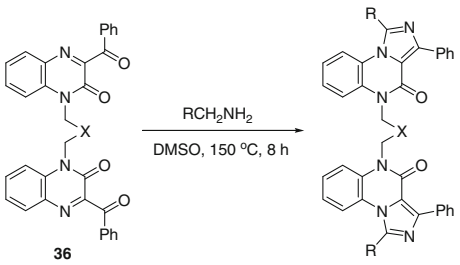


34a-h **12a, 35a-l** (44-98%)

34 R^1 = H (**a,b**): R^2 = Ph (**a**), Me (**b**);
R^2 = Ph (**c-h**): R^1 = Me (**c**), Et (**d**), *n*-Pr (**e**), *n*-C_6H_{13} (**f**), *n*-C_9H_{19} (**g**), *n*-$C_{18}H_{37}$ (**h**)
35 R^1 = H (**a-d**):
R^2 = R^3 =Ph (**a**), R^2 = Ph, R^3 =Py (**b**), R^2 = Me, R^3 = Ph (**c**), R^2 = Me, R^3 = Py-3 (**d**);
R^1 = Me, R^2 = R^3 = Ph (**e**); R^1 = Et, R^2 = Ph (**f,g**): R^3 = Ph (**f**), R^3 = Py-3 (**g**);
R^1 = *n*-Pr, R^2 = Ph (**h,i**): R^3 = Ph (**h**), R^3 = Py-3 (**i**);
R^2 = Ph, R^3 = Py-3 (**j-l**): *n*-C_6H_{13} (**j**), *n*-C_9H_{19} (**k**), *n*-$C_{18}H_{37}$ (**l**)

Scheme 4.17 Cyclization of 3-benzoyl- and 3-acetyl-quinoxalin-2(1*H*)-ones when exposed to compounds with aminomethyl moiety

Scheme 4.18 Synthesis of podands with the terminal 1,3-diphenyl- and 1-pyridyl-3-phenylimidazo[1,5-*a*]quinoxalin-4-on-5-yl platforms



36 **37a-g** (48-79%)

37 R = Ph (**a-e**): X = CH_2OCH_2 (**a**), $(CH_2OCH_2)_2$ (**b**), $(CH_2OCH_2)_3$ (**c**), $(CH_2)_4$ (**d**), C_6H_4-1,3 (**e**);
R = Py-3 (**f,g**): X = $(CH_2)_4$ (**f**), $(CH_2OCH_2)_3$ (**g**)

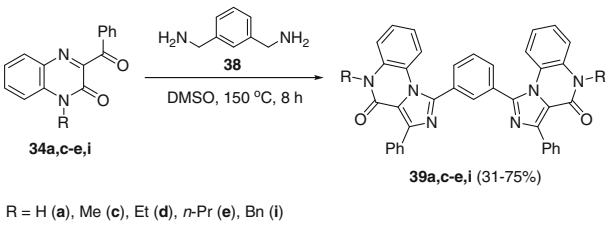
(Scheme 4.18) (Mamedov et al. 2004, 2009; Kalinin and Mamedov 2008b; Kalinin et al. 2013).

The second approach to the synthesis of bis(imidazoquinoxaline)s is based on the use of a compound containing two aminomethyl moieties, 1,3-di(aminomethyl) benzene **38**.

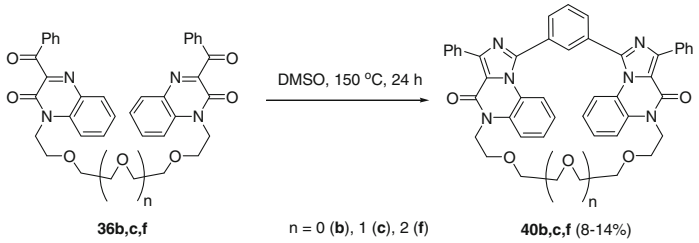
It reacts with 3-benzoylquinoxalin-2-ones **34a**, **c–e**, **i** to give 1,3-bis(imidazo[1,5-*a*]quinoxalin-4-on-1-yl)benzenes **39a**, **c–e**, **i** (Mamedov et al. 2004, 2009; Kalinin and Mamedov 2008b). These compounds are of interest as bidentate chelating agents and precursors of macrocycles (Scheme 4.19).

An original method of constructing new types of crown ether derivatives **40b**, **c**, **f** is a combination of the above approaches to the synthesis of bis(imidazo[1,5-*a*]quinoxaline)s (Mamedov et al. 2009). However, from compounds **36b**, **c**, **f**, these macrocycles are obtained in low yields. The yield of products **40** insignificantly increases when the reaction is carried out in the presence of alkali metal salts ($LiClO_4$, NaCl, KI) as template agents (Scheme 4.20) (Mamedov et al. 2009).

The method of formation of the N(10)–C(1) and N(2)–C(3) bonds suggested by the authors of this review (Mamedov et al. 2009) has been successfully used for

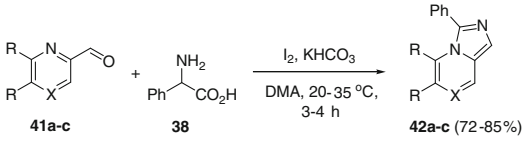


Scheme 4.19 Synthesis of 1,3-bis(imidazo[1,5-*a*]quinoxalin-4-on-1-yl)benzenes



Scheme 4.20 Synthesis of diimidazoquinoxalinabenzenecyclophanes

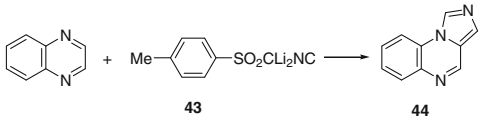
Scheme 4.21 Reactions of quinoxaline-, quinoline- and pyridine-2-carbaldehydes with phenylglycine



imidazo[*a*]annulation of quinoxaline, quinoline, and pyridine derivatives (Wang et al. 2012). The starting compounds are quinoxaline-**41a**, quinoline-**41b** and pyridine-2-carbaldehydes **41c** (instead of 3-benzoylquinoxalinone derivatives) and phenylglycine (instead of benzyl- and picolylamines). The reactions have been carried out under milder conditions than in Mamedov et al. (2009) (DMSO, 150 °C) and have afforded products **42a–c** in rather high yields (Scheme 4.21).

4.2.6 Methods of Formation of the N(10)–C(1) and C(3)–C(3a) Bonds (Variant D_Q)

All known $\mathbf{D_Q}$-type methods of synthesis of imidazoquinoxalines (see Fig. 4.3) involve the reaction of quinoxaline derivatives with synthetic equivalents of the C^{2-}–(R)–N=C^{+} fragment; as such, methyl isocyanides are usually used. The principle



Scheme 4.22 Synthesis of imidazo[1,5-*a*]quinoxaline from quinoxaline and dilithium derivative of *p*-toluenesulfonylmethyl isocyanide

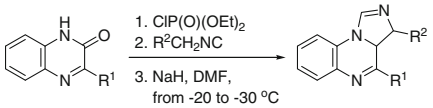
possibility of implementing this approach was demonstrated for the first time in 1980 by the reaction of unsubstituted quinoxaline with dilithium derivative **43**, readily generated from *p*-toluenesulfonylmethyl isocyanide (TsMIC) under the action of two *n*-BuLi equivalents in THF at −70 °C (Nispen et al. 1980). The yield of imidazo[1,5-*a*] quinoxaline **44** was 30 % (Scheme 4.22).

Quinoxalin-2(1*H*)-ones of different structure react with methyl isocyanides under the action of bases to form imidazo[1,5-*a*]quinoxaline derivatives (Hansen and Waetjen 1989a, b, c, 1990, 1991; Jacobsen et al. 1996a, b, 1999; Mickelson et al. 1996; Nispen et al. 1980; Waetjen 1987; TenBrink et al. 1992, 1993, 1994, 1996; Wang et al. 2012). The reaction is usually carried out in the presence of diethyl chlorophosphite at low temperatures. The in situ formed diethyl quinoxalinylphosphonate (see below) readily reacts with substituted methyl isocyanides, and 1,3-dipolar cycloaddition thereby leads to annulation of the imidazole ring. By this method, quinoxalinones **45a**, **b** have been converted into imidazo[1,5-*a*] quinoxalines **46a–h** with different substituents in the 3-position (Scheme 4.23) (Hansen and Waetjen 1989a, 1990).

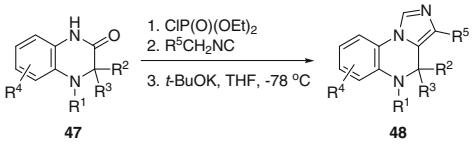
The reaction of substituted dihydroquinoxalin-2(1*H*)-ones **47** under these conditions leads to corresponding dihydroimidazoquinoxalines **48** (Waetjen 1987; TenBrink et al. 1992, 1994, 1996; Jacobsen et al. 1996a, b, 1999). The number of imidazo[1,5-*a*]quinoxaline derivatives thus synthesized amounts to several hundreds (Scheme 4.24).

Tricyclic compounds **49a–d** and **50a–d**, containing the quinoxalin-2(1*H*)-one moiety with the carbonyl group at the C(4) atom reacts with isocyanides in the presence of potassium *tert*-butoxide to form tetracycles **51a–d** and **52a–d**, respectively (Schemes 4.25 and 4.26) (TenBrink et al. 1994; Mickelson et al. 1996). The latter have been synthesized both in the racemic form **52a**, **d** and as optical isomers with the *S* (**52b**) and *R* configuration (**52c**) of the asymmetric center.

Scheme 4.23 Synthesis of imidazo[1,5-*a*]quinoxalines from quinoxalin-2(1*H*)-ones when exposed to methyl isocyanides in the presence of diethyl chlorophosphite



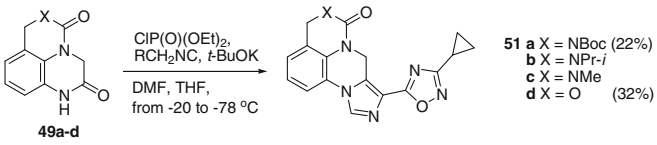
45 R^1 = H (**a**), Me (**b**)
46 R^1 = H (**a-c**): R^2 = CO_2Et (**a**), CO_2Pr-*i* (**b**), CO_2Bu-*t* (**c**); R^1 = Me (**d-h**): R^2 = CO_2Et (**d**), CO_2Pr-*i* (**e**), CO_2Bu-*t* (**f**), 5-cyclopropyl-1,2,4-oxadiazol-3-yl (**g**), 5-methyl-1,2,4-oxadiazol-3-yl (**h**)



47 **48**

R^1 = Ac, Bz, Boc, C(O)Et, C(O)CF_3, C(O)NMe_2, C(O)NEt_2, pyrrolidinocarbonyl, morpholinocarbonyl, piperidinocarbonyl, 2-furylcarbonyl, *etc.*
R^2, R^3 = H, Me
R^4 = H, Me, F, Cl
R^5 = 5-X-1,2,4-oxadiazol-3-yl (X = Et, *i*-Pr, *c*-C_3H_5), CO_2Bu-*t*, Ar
Boc = C(O)OBu-*t*

Scheme 4.24 Synthesis of dihydroimidazo[1,5-*a*]quinoxalines from dihydroquinoxalin-2(1*H*)-ones when exposed to methyl isocyanides in the presence of diethyl chlorophosphite

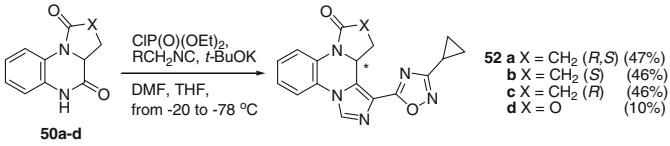


49a-d

R = 3-cyclopropyl-1,2,4-oxadiazol-5-yl

51 a X = NBoc (22%)
b X = NPr-*i*
c X = NMe
d X = O (32%)

Scheme 4.25 The use of quinoxalin-2(1*H*)-one moiety for the synthesis of condensed imidazo [1,5-*a*]quinoxaline derivatives



50a-d

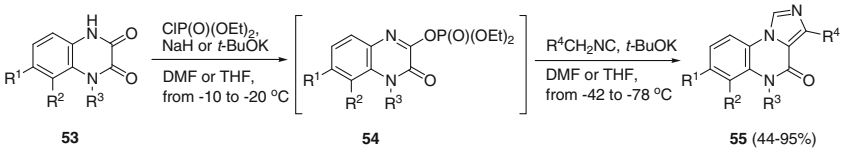
R = 3-cyclopropyl-1,2,4-oxadiazol-5-yl

52 a X = CH_2 (*R,S*) (47%)
b X = CH_2 (*S*) (46%)
c X = CH_2 (*R*) (46%)
d X = O (10%)

Scheme 4.26 The use of quinoxalin-2(1*H*)-one moiety for the synthesis of condensed imidazo [1,5-*a*]quinoxaline derivatives

A method of synthesis of imidazoquinoxalin-4-ones that affords these heterocyclic systems with different substituents in the 3-, 5-, 6- and 7-positions has been well developed (Waetjen 1987; Waetjen and Hansen 1988, 1990, 1991; Hansen and Waetjen 1989b, c; Jacobsen et al. 1996a; TenBrink et al. 1993). The method is based on the reaction of quinoxaline-2,3-dione derivatives **53** with diethyl chlorophosphite leading to diethyl quinoxalinyl phosphates **54**. The latter, without isolation, are introduced into the reaction with substituted methyl isocyanides in the presence of a base leading to products **55** (Scheme 4.27).

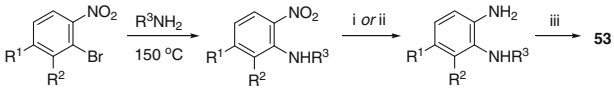
Quinoxaline-2,3-diones **53**, containing necessary substituents in the benzo moiety, are synthesized in three stages from *o*-halonitrobenzenes. The transformations involve the substitution of an amino group for the halogen atom to form compounds **56**, the reduction of the nitro group to the amino group and



53 **54** **55** (44-95%)

55 R^1, R^2 = H, Cl, F, Me
R^3 = Me, *i*-Pr, *t*-Bu, Bn, $PhCH_2CH_2$, 2-$PyCH_2$, 2-$MeOC_6H_4CH_2$, *c*-$[O(CH_2CH_2)_2N]CH_2CH_2$, *c*-$C_3H_5CH_2CH_2$
R^4= CO_2Et, 5-cycloprop-1-yl, 2,4-oxadiazol-3-yl, 3-cyclopropyl-1,2,4-oxadiazol-5-yl, C_6H_4X (X = H, F, Cl, OMe, CF_3)

Scheme 4.27 The use of quinoxalin-2(1*H*)-one moiety for the synthesis of the 3-, 5-, 6- and 7-substituted imidazo[1,5-*a*]quinoxalines



56 **57**

i = H_2, 5% Pd/C, EtOH; ii = H_2, 5% Pt/S/C, EtOH; iii = $EtO_2CC(O)Cl$ or $(COCl)_2$, EtN(Pr-*i*)$_2$, PhMe

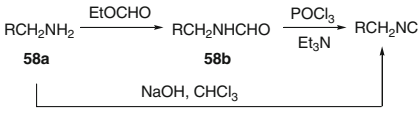
Scheme 4.28 Synthesis of quinoxaline-2,3-diones, containing substituents in the benzo moiety

condensation of substituted diaminobenzenes **57** with oxalyl chlorides (Scheme 4.28) (Jacobsen et al. 1996a).

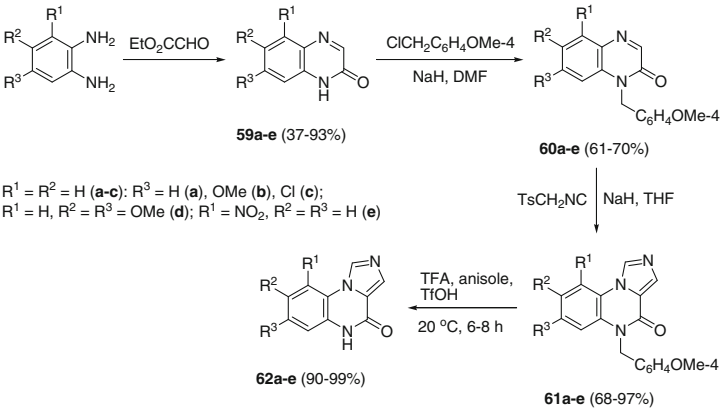
Two classical methods based on methylamines **58a** have been developed for preparation of substituted methyl isocyanides–the second component of the reaction shown in Scheme 4.28. The first method consists of one stage, namely, treatment of amines with chloroform in the presence of alkalis; the second method consists of two stages. The reaction with ethyl formate leads to formamides **58b**, which are then dehydrated by treating with phosphorus oxochloride in the presence of triethylamine (Scheme 4.29) (Jacobsen et al. 1996a).

Two decades after the first example of annulation of the imidazole moiety (Nispen et al. 1980) to bond *c* of quinoxaline under the action of dilithium salt **43**, a new procedure has been suggested in which the initial compounds are quinoxalinones **59** (Barrish and Spergel 2001; Chen et al. 2001, 2002a; Hazeldine et al. 2005). Protected *N*-(4-methoxybenzyl)quinoxalinones **60** are introduced into the reaction with TsMIC in THF in the presence of NaH, which leads to imidazoquinoxaline **61** in high, sometimes quantitative, yields. The protective group is removed under the action of trifluoroacetic acid (TFA), anisole and trifluoromethanesulfonic acid (TfOH). This method is simple and enables the

Scheme 4.29 Synthesis of substituted methyl *iso*-cyanides



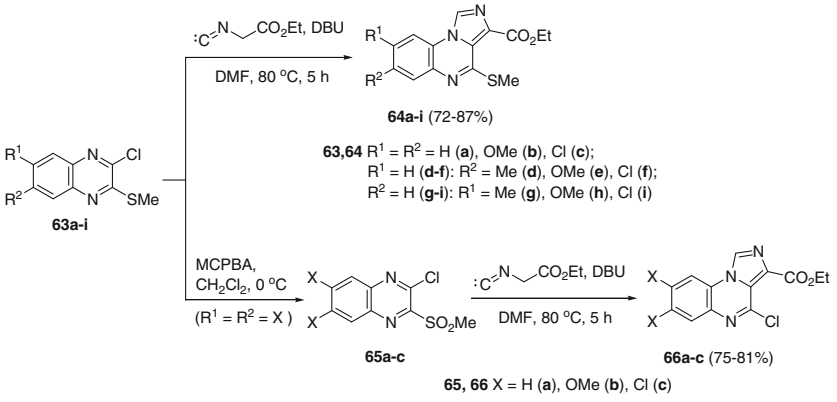
58a **58b**



Scheme 4.30 The use of bond *c* of quinoxalinone for the synthesis substituted imidazo[1,5-*a*] quinoxalines

synthesis of different initial *N*(1)-alkylated quinoxalin-2(1*H*)-ones through condensation of 1,2-DABs and ethyl glyoxalate with subsequent introduction of the protective *p*-methoxybenzyl group. The method has opened a new way to the synthesis of numerous imidazo[1,5-*a*]quinoxalines **62** with the free 1- and 3-positions (Scheme 4.30).

When quinoxaline has an easily leaving group in the 2-position, annulation of the imidazole ring according to variant $\mathbf{D_Q}$ can also occur, which is demonstrated by Scheme 4.31 (Sundaram et al. 2007). The reaction of 2-methylsulfanyl-3-chloroquinoxalines **63a–i** with ethyl isocyanoacetate leads to



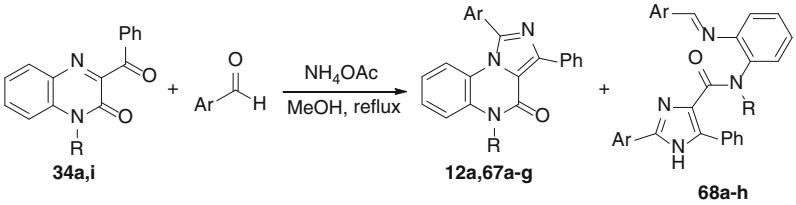
Scheme 4.31 The reactions of 2-methylsulfanyl-3-chloroquinoxalines with ethyl *iso*-cyanoacetate

4-methylsulfanylimidazoquinoxalines **64a–i**, whereas the reaction of the products of oxidation of compounds **63a–c**, sulfones **65a–c**, gives 4-chloroimidazoquinoxalines **66a–c** (Chen et al. 2002a).

4.2.7 *Method of Formation of the N(10)–C(1), C(1)–N(2), and N(2)–C(3) Bonds (Variant E1$_Q$)*

It should be noted that the examples of **E**-type formation of bonds in imidazo[1,5-*a*]quinoxalines are limited to variant **E1$_Q$**. The three-component reaction of 3-benzoylquinoxalin-2(1*H*)-one **34a** with aromatic aldehydes and NH_4OAc in boiling methanol is the only example of **E$_Q$**-type synthesis of the imidazo[1,5-*a*]quinoxaline system (Mamedov et al. 2011). This reaction leads not only to imidazo[1,5-*a*]quinoxaline derivatives **12a** and **67a–g** but also to 2,4,5-trisubstituted imidazoles **68a–h**, sometimes as major products. It should be noted that the reaction of *N*-alkylated 3-benzoylquinoxalin-2(1*H*)-one **34i** yields only imidazo[1,5-*a*]quinoxaline **67g**. As distinct from variant **C1$_Q$** of synthesis of imidazo[1,5-*a*]quinoxalines where aminomethyl derivatives are used to introduce the C(1)–N(2) fragment into 3-benzoylquinoxalin-2(1*H*)-one, in this case the reaction involves

Table 4.2 Three-component reaction of 3-benzoylquinoxalin-2(1*H*)-one with aromatic aldehydes and NH_4OAc for the synthesis of imidazo[1,5-*a*]quinoxaline system



34	R	Ar	Products [Yield (%)]
34a	H	Ph	**12a** (26) + **68a** (49)
34a	H	C_6H_4Br-4	**67a** (33) + **68b** (47)
34a	H	$C_6H_4NO_2$-4	**67b** (17) + **68c** (47)
34a	H	C_6H_4F-4	**67c** (26) + **68d** (45)
34a	H	C_6H_4Cl-4	**67d** (28) + **68e** (40)
34a	H	C_6H_4I-4	**67e** (29) + **68f** (44)
34a	H	Py-3	**67f** (42) + **68g** (38)
34i	*n*-Bu	Ph	**67g** (42) + **68h** (traces)

different substituted aldehydes, including pyridine-3-carbaldehyde, and inexpensive and readily available ammonium acetate. This approach is attractive since it enables the introduction of a definite substituent in any position of imidazo[1,5-*a*]quinoxalines under relatively mild conditions (Table 4.2).

4.3 Synthesis of Imidazo[1,5-*a*]quinoxalines Based on Imidazole Derivatives

Design of the imidazo[1,5-*a*]quinoxaline system on the basis of imidazole derivatives has been much less studied than the synthesis based on quinoxaline derivatives. Three variants of assembly of such a tricyclic system are mainly used: intramolecular cyclization of imidazole derivatives with formation of the C(4)–N(5) and C(9a)–N(10) bonds (variants $\mathbf{A2_I}$ and $\mathbf{A4_I}$, respectively) and intermolecular condensation with equivalents of monoatomic carbon synthons with the simultaneous formation of the C(3a)–C(4) and C(4)–N(5) bonds (variant $\mathbf{B1_I}$) (Fig. 4.4). Other routes are represented by single examples.

4.3.1 Method of Formation of the C(3a)–C(4) Bond (Variant $A1_I$)

As distinct from imidazo[1,2-*a*]quinoxaline derivatives for which the method of construction of the heterocycle through the formation of the C(3a)–C(4) bond is basic (see Sect. 4.5.1), there are only two publications describing the $\mathbf{A1_I}$-type synthesis of representatives of the tricyclic imidazo[1,5-*a*]quinoxaline system (Malamas et al.

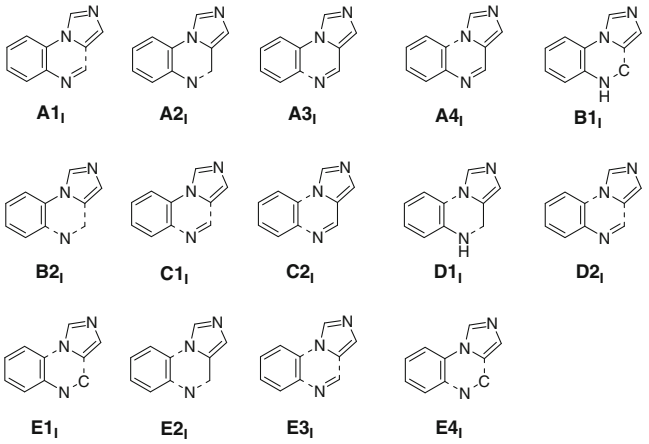
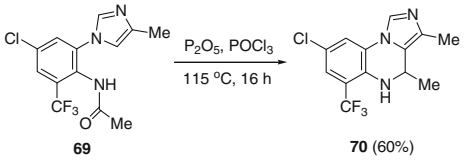


Fig. 4.4 Possible variants of construction of the imidazo[1,5-*a*]quinoxaline system on the basis of imidazole derivatives



Scheme 4.32 Intramolecular cyclization of *N*-(4-chloro-2-(4-methyl-1*H*-imidazol-1-yl)-6-(trifluoromethyl)phenyl)acetamide when exposed to the mixture of phosphorus(V) oxide and oxochloride

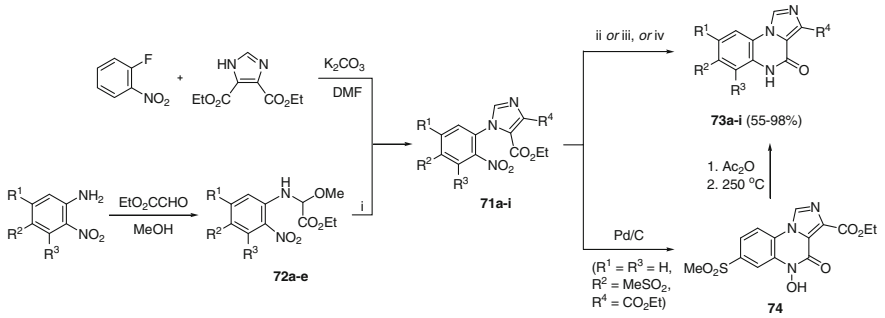
2010, 2011b). The condensation of acetamide **69** in a mixture of phosphorus(V) oxide and oxochloride on heating leads to imidazo[1,5-*a*]quinoxaline **70** (Scheme 4.32).

4.3.2 Methods of Formation of the C(4)–N(5) Bond (Variant A2$_1$)

Reductive cyclization of 1-(2-nitrophenyl)-5-ethoxycarbonylimidazoles **71** is used rather often for constructing the imidazo[1,5-*a*]quinoxaline ring. Compounds **71** are synthesized by two methods: (1) from *o*-fluoronitrobenzenes by the reaction with 4,5-diethoxycarbonylimidazole in the presence of K_2CO_3 (Lee and Brown 1983, 1984) or Cs_2CO_3 (Pierre et al. 2012) in DMF; (2) in two stages–by the reaction of *o*-nitroanilines with ethyl glyoxylate followed by cyclization of the resulting α-methoxy-α-(2-nitroanilino)acetates **72** (Chen et al. 2004a, b). The cyclization of compounds **71** gives imidazo[1,5-*a*]quinoxalines **73** (R^2 = H, OMe) (Lee and Brown 1983; Chen et al. 2004a, b; Borchardt et al. 2011b; Kim et al. 2011; Pierre et al. 2012). Once the benzene ring of molecule **71** has the acceptor methylsulfonate group, the reduction mainly leads to 5-hydroxyimidazoquinoxaline **74**, which is then converted in two stages into imidazoquinoxaline **73b** (acylation with acetic anhydrides and subsequent thermolysis) (Lee and Brown 1983, 1984).

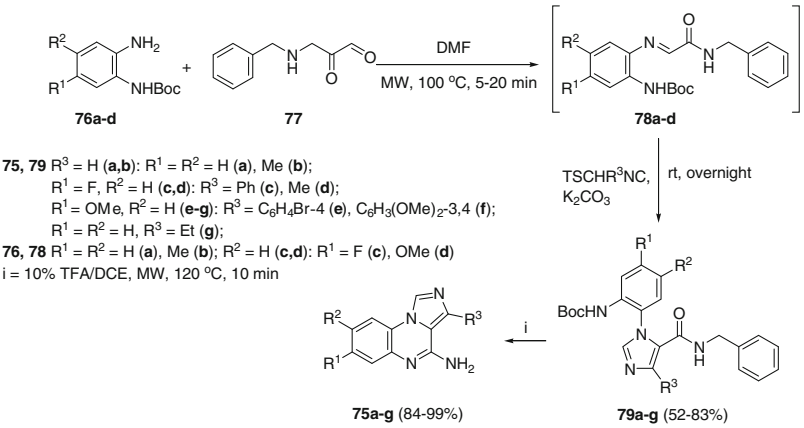
The reduction with sodium dithionite in aqueous acetic acid gives imidazoquinoxaline **73c** in nearly quantitative yield (Lee and Brown 1984). It should be noted that this method is universal for synthesis of derivatives of other heterocyclic systems, in particular, thiazolo[3,4-*a*]- (Adegoke and Alo 1983), pyrrolo[1,2-*a*]- (Silvestri et al. 2000) and indolo[1,2-*a*]quinoxalines (Basanagoudar et al. 1991). Their formation depends on the type of heterocyclic moiety in compounds **71** (Scheme 4.33).

A convenient method of synthesis of pharmacologically attractive imidazoquinoxaline derivatives **75a–g** has been described (DeMoliner and Hulme 2012b). The method involves the three-component reaction of *N*-Boc-*o*-phenylenediamines **76a–d** with glyoxylic acid derivatives, namely, with ethyl glyoxylate (see Sect. 4.4) and benzylglyoxylamide **77**, with the participation of tosylmethyl isocyanides. The reaction is carried out under microwave irradiation [the Van Leusen and Van Leusen modification (2012)]. It is likely that, first, the condensation of aldehyde at the free amino group of compounds **76a–d** leads to imines **78a–d**, which are



72 $R^1 = R^2 = OMe$, $R^3 = H$ (**a**); $R^1 = NHMe$, $R^3 = H$ (**b-d**); $R^2 = H$ (**b**), F (**c**), Cl (**d**); $R^1 = R^2 = H$, $R^3 = CO_2Et$ (**e**);
71, 73 $R^1 = R^3 = H$, $R^4 = CO_2Et$ (**a,b**): $R^2 = H$ (**a**), SO_2Me (**b**); $R^1 = R^2 = OMe$, $R^3 = R^4 = H$ (**c**);
$R^2 = R^3 = H$, $R^1 = Cl$, $R^4 = CO_2Et$ (**d**); $R^1 = R^2 = R^4 = H$ (**e,i**): $R^3 = Cl$ (**e**), CO_2Et (**i**);
$R^1 = NHMe$, $R^3 = R^4 = H$ (**f-h**): $R^2 = H$ (**f**), F (**g**), Cl (**h**)
i = $TsCH_2NC$, K_2CO_3, EtOH, 50 °C, 4 h; ii = Pd/C, EtOH; iii = Fe, AcOH, 105 °C, 6-12 h; iv = $Na_2S_2O_4$, AcOH, H_2O, 105 °C, 6 h

Scheme 4.33 Synthesis and intramolecular cyclization of substituted ethyl 1-(2-nitrophenyl)-1*H*-imidazole-5-carboxylates



75, 79 $R^3 = H$ (**a,b**): $R^1 = R^2 = H$ (**a**), Me (**b**);
$R^1 = F$, $R^2 = H$ (**c,d**): $R^3 = Ph$ (**c**), Me (**d**);
$R^1 = OMe$, $R^2 = H$ (**e-g**): $R^3 = C_6H_4Br$-4 (**e**), $C_6H_3(OMe)_2$-3,4 (**f**);
$R^1 = R^2 = H$, $R^3 = Et$ (**g**);
76, 78 $R^1 = R^2 = H$ (**a**), Me (**b**); $R^2 = H$ (**c,d**): $R^1 = F$ (**c**), OMe (**d**)
i = 10% TFA/DCE, MW, 120 °C, 10 min

Scheme 4.34 Synthesis and intramolecular cyclization of *tert*-butyl 2-(5-(benzylcarbamoyl)-1*H*-imidazol-1-yl)phenylcarbamates

cyclized to give imidazole derivatives **79a–g**. Removal of the Boc protective group from the nitrogen atom of compounds **79a** promotes further cyclization, which occurs either spontaneously with formation of heterocycle **75a** or under microwave irradiation in acid conditions. In the latter case, compounds **75b–g** are formed. It should be noted that the formation of the imidazoquinoxaline system by this method occurs rapidly and is highly effective (Scheme 4.34).

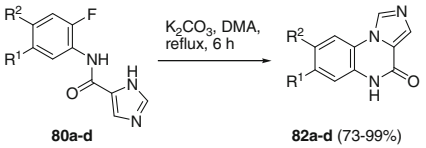
The strategy of Van Leusen and Van Leusen (2012) served as a basis for the development of a one-pot process, which made it possible to synthesize imidazo[1,5-*a*]quinoxalines with the use of phenylglyoxaldehyde instead of benzylglyoxylamide (see Sect. 4.4) (DeMoliner and Hulme 2012a).

4.3.3 Methods of Formation of the C(9a)–N(10) Bond (Variant $A4_I$)

The intramolecular nucleophilic substitution of the fluorine atom in 1*H*-imidazole-5-carboxyl-2-fluoroanilides **80a–d** and **81a–h** in the presence of a base leads to imidazo[1,5-*a*]-quinoxalines containing a hydrogen atom **82a–d** (Scheme 4.35) or aminocarbonylmethyl group in the 5-position **83a–h** (Scheme 4.36) according to variant $\mathbf{A4_I}$ (see Fig. 4.4) (Barrish and Spergel 2001; Norris et al. 2001; Spatz et al. 2007; Moarbess et al. 2008b). The cyclization of anilides **80a–d** proceeds in boiling dimethylacetamide for 6 h, and the cyclization of derivatives **81a–h** in DMF under microwave irradiation at 150 °C for 20 min gives the products in high yields.

Anilides **80** have been synthesized through acylation of *o*-fluoroanilines by carbonylimidazole dimer (diimidazo[1,5-*a*:1,5-*d*]-pyrazine-5,10-dione, **84a**) in the presence of sodium hexamethyldisilazide (NaHMDS) (Scheme 4.37) (Barrish and Spergel 2001; Norris et al. 2001).

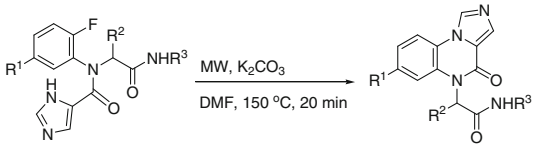
Compounds **81** are synthesized by the Ugi reaction, which is a multicomponent process involving *o*-fluoroaniline, aldehyde, isocyanide, and 1*H*-imidazole-5-carboxylic acid. The reaction is initiated by condensation of aniline with aldehyde leading to the corresponding imine, which successively reacts with the acid and isocyanide to give target compounds **81**. Trifluoroethanol is used as a solvent in this reaction (Scheme 4.38) (Spatz et al. 2007).



80a-d **82a-d** (73-99%)

R^1 = H (**a**,**b**): R^2 = H (**a**), Br (**b**); R^1 = Br, R^2 = F (**c**); R^1 = F, R^2 = Br (**d**)

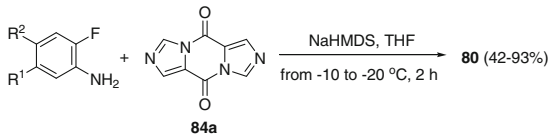
Scheme 4.35 Cyclization of *N*-(2-fluorophenyl)-1*H*-imidazole-5-carboxamides in boiling dimethylacetamide



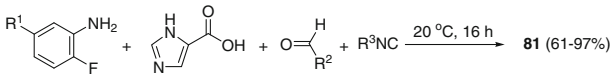
81a-h **83a-h** (37-92%)

R^1 = H, R^2 = *c*-C_3H_5 (**a-d**): R^3 = *t*-Bu (**a**), C_6H_4OMe-4,(**b**), $CH_2C_6H_4OMe$-4 (**c**), Me (**d**);
R^1 = R^2 = H (**e,f**): R^3 = $CH_2C_6H_4OMe$-4(**e**), *t*-Bu (**f**);
R^1 = H, R^2 = C_6H_4OMe-4,R^3 = *t*-Bu (**g**); R^1 = CF_3, R^2 = *c*-C_3H_5, R^3 = *t*-Bu (**h**)

Scheme 4.36 Cyclization of *N*-(2-fluorophenyl)-1*H*-imidazole-5-carboxamides in DMF under microwave irradiation



Scheme 4.37 Synthesis of *N*-(2-fluorophenyl)-1*H*-imidazole-5-carboxamides through the acylation of *o*-fluoroanilines by carbonylimidazole dimmer

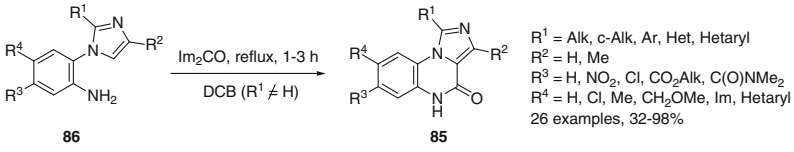


Scheme 4.38 Synthesis of *N*-(2-fluorophenyl)-1*H*-imidazole-5-carboxamides by the Ugi reaction

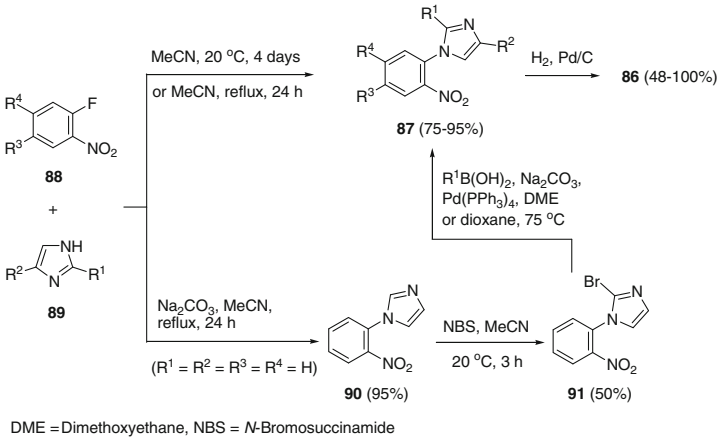
4.3.4 Methods of Formation of the C(3a)–C(4) and C(4)–N(5) Bonds (Variant B1$_I$)

An efficient **B1$_I$**-type method of synthesis of imidazo[1,5-*a*]quinoxalines **85** is the reaction of 2-(1*H*-imidazol-1-yl)aminobenzenes **86** with 1,1′-carbonyldiimidazole (Scheme 4.39) (Davey et al. 1991; Colotta et al. 1995; Ohmori et al. 1997; Davey 1999; Okada et al. 2009; Kaizawa et al. 2011). The reaction proceeds in boiling *o*-dichlorobenzene (DCB) to give target products in moderate to high yields.

Necessary starting compounds **86** are synthesized by either a two- or a four-stage method. The last stage in both cases is the catalytic reduction of 1-(2-nitrophenyl)-imidazoles **87**. In the first method, compounds **87** are formed through the nucleophilic substitution of the fluorine atom in *o*-fluoronitrobenzenes **88** by imidazoles **89** (Davey et al. 1991; Colotta et al. 1995; Ohmori et al. 1997; Davey 1999). The second method consists of the following stages: (a) the arylation of imidazole with *o*-fluoronitrobenzene in the presence of sodium carbonate, (b) the bromination of 2-nitrophenylimidazole **90** with bromosuccinamide, (c) the introduction of an alkyl or aryl fragment into the imidazole ring of 2-bromo derivative **91** by the Suzuki cross-coupling reaction leading to products **87** (Scheme 4.40) (Moarbess et al. 2008b). The availability of the starting compounds, the ease of each stage and high yields allow easy variation of substituents in the 2-position of the imidazole ring, which leads



Scheme 4.39 Synthesis of imidazo[1,5-*a*]quinoxalines by interaction of 2-(1*H*-imidazol-1-yl) aminobenzenes with 1,1′-carbonyldiimidazole

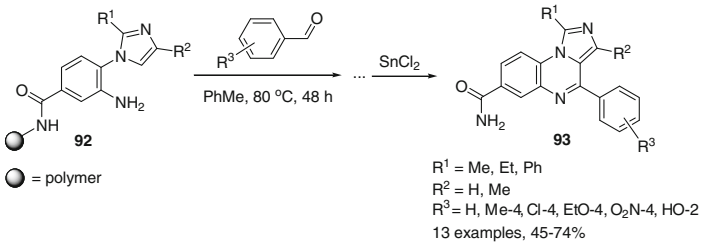


Scheme 4.40 Synthesis and cyclization of 1-(2-nitrophenyl)-1*H*-imidazoles

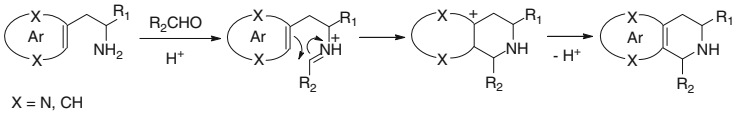
to different 1-substituted imidazo[1,5-*a*]-quinoxalines **85** (Davey et al. 1991; Colotta et al. 1995; Ohmori et al. 1997; Davey 1999; Okada et al. 2009; Kaizawa et al. 2011).

A structural specific feature of 2-(1*H*-imidazol-1-yl)aminobenzene derivatives **92** makes it possible to use them in the Pictet–Spengler reaction (Jiang et al. 2002; Tsuji et al. 2003) with aldehydes. However, as distinct from β-arylethylamines (key compounds of the Pictet–Spengler reaction) giving tetrahydroisoquinoline derivatives, these compounds form corresponding imidazo[1,5-*a*]quinoxalines **93** (Scheme 4.41) (Kundu et al. 2005). The reaction occurs in the solid phase, and all stages of formation of 2-(1*H*-imidazol-1-yl)aminobenzene derivatives **92** are carried out with the participation of a fluoronitrobenzene derivative attached to a polymer substrate through the carbamoyl bond. Tin chloride is used as a reducing agent.

An efficient method of selective synthesis of the oxidized and reduced forms of imidazo[1,5-*a*]quinoxalines via modified Pictet–Spengler reaction of 2-imidazolyl anilines with arylaldehydes (the possible mechanism is shown in Scheme 4.42) has been described (Verma et al. 2013). The reaction proceeds under mild conditions



Scheme 4.41 The Pictet–Spengler reaction for the synthesis of imidazo[1,5-*a*]quinoxalines from 2-(1*H*-imidazol-1-yl)aminobenzene derivatives



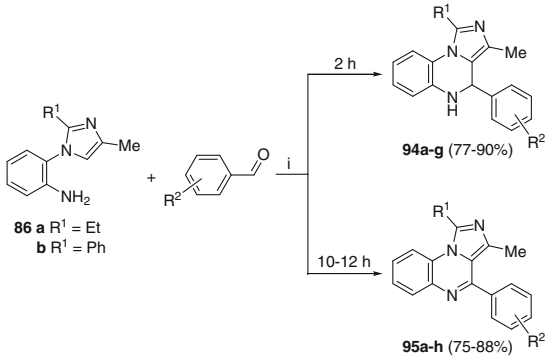
Scheme 4.42 Plausible mechanism of the Pictet–Spengler reaction

and affords the products in high yields if the imidazole ring contains electron-donating substituents in the 2- and 4-positions, which facilitates electrophilic aromatic substitution at the 5-position of imidazole.

The reaction of 2-(1*H*-imidazol-1-yl)aminobenzenes **86a**, **b** with substituted benzaldehydes in the presence of benzotriazole and TsOH in toluene for 2 h leads to dihydroimidazoquinoxalines **94a–g** in high yield (Scheme 4.43) (Verma et al. 2013). The best condition for the formation of imidazoquinoxalines **95a–h** is to increase the reaction duration to 12 h, which ensures the complete conversion of the intermediate dihydro derivative. Thus, varying the reaction time allows one to stop the reaction after the formation of compound **94** or **95**.

Both 4,5-dihydro derivatives **94** and imidazo[1,5-*a*]quinoxalines **95** are obtained in high yields and under mild conditions. Aniline **86a** with two electron-donating groups in the imidazole ring reacts more readily than aniline **86b**, containing only the methyl group in this ring. The reaction of *p*-bromobenzaldehyde with *N*-(2-aminophenyl)imidazole ($R^1 = R^2 = H$ in formula **86**, see Scheme 4.39) does not lead to corresponding dihydroimidazo[1,5-*a*]quinoxaline **94**.

At the same time, aldehydes with electron-donating substituents and halogen atoms ensure the highest yield of imidazo[1,5-*a*]quinoxalines **95** (Verma et al. 2013).



94 R^1 = Et (**a-g**): R^2 = Br-4 (**a**), O_2N-4 (**b**), 2,4-Cl_2 (**c**), Cl-3 (**d**), O_2N-3 (**e**), MeO-3(**f**); R^1 = H, R^2 = MeO-4 (**g**)
95 R^1 = Et (**a-c**): R^2 = Br-4(**a**), F-4 (**b**), Me-4(**c**); R^1 = H (**d-g**): O_2N-4 (**d**), NC-4 (**e**), F_3C-4 (**f**), O_2N-3 (**g**), MeO-3(**h**)
i = benzotriazole, 10% TsOH, PhMe, 25 °C

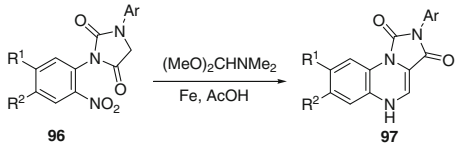
Scheme 4.43 Reaction of 2-(1*H*-imidazol-1-yl)aminobenzenes **86a**, **b** with substituted benzaldehydes

The use of 1-(*o*-nitrophenyl)imidazole-2,5-diones **96** and dimethylformamide dimethyl acetal has been patented as another source of structural fragments necessary for $\mathbf{B1_I}$-type construction of the tricyclic system (Shaw 1992, 1993a, b, c, 1995). The condensation of these reactants in acetic acid in the presence of iron powder has been used to obtain a large number of imidazoquinoxaline-2,3-diones **97** with a variety of substituents. Unfortunately, the yields of the products have not been specified in patents (Shaw 1992a, b, c, 1995) (Scheme 4.44).

Compounds **96** have been synthesized from 2-nitrophenyl isocyanates **98** through the formation of corresponding urea derivatives **99**: they react with acetic chloride to give compounds **100**, which undergo cyclization to yield compounds **96**. This method (Shaw 1992, 1993a, b, c, 1995), as well as variant $\mathbf{A3_Q}$ using quinoxaline derivatives (Ahmad et al. 1964), has been developed in detail precisely for the synthesis of 2,3-dioxoimidazoquinoxalines (Scheme 4.45).

The reaction of 1-(*o*-methylaminophenyl)imidazole-2,5-dione **101** with ethyl formate under the action of sodium yields 1,3-dioxoimidazoquinoxaline **102**, which is reduced by tin in a mixture of acetic and hydrochloric acids to give imidazoquinoxaline **103** (Scheme 4.46) (King and Clark-Lewis 1951).

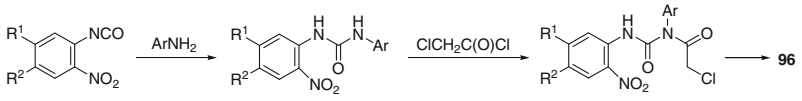
When elucidating the structure of the compound resulting from the alkaline hydrolysis of the product of the reaction of alloxan **104** with *o*-dimethylaminoaniline, Rudy and Cramer (1939) found a new method of synthesis of dihydroimidazoquinoxaline **103**. This method is a promising approach to synthesis of spiro-fused quinoxaline **105** (Scheme 4.47).



96 **97**

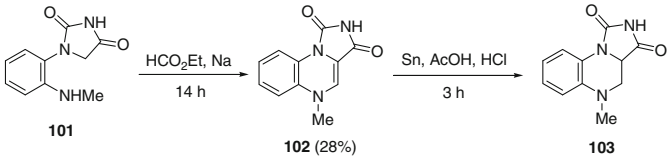
R^1, R^2 = H, Me, Cl, Br, CO_2Et
Ar = C_6H_4X (X = H, F, Cl, Br, Me, Et, *n*-Pr, OMe, OEt, OPr-*n*, OPr-*i*, OAc, NH_2), C_6H_3XY (X = F, Br; Y = Me, OEt), Th-2

Scheme 4.44 Reaction of 1-(*o*-nitrophenyl)imidazole-2,5-diones dimethylformamide dimethyl acetal in acetic acid in the presence of iron powder

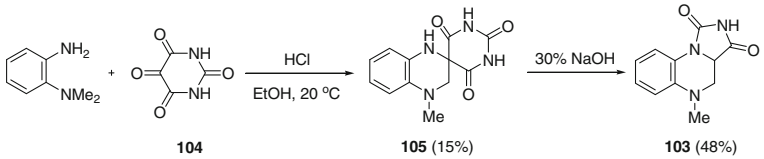


98 **99** **100**

Scheme 4.45 Synthesis and cyclization of 2-chloro-*N*-(2-nitrophenylcarbamoyl)-*N*-arylacetamides



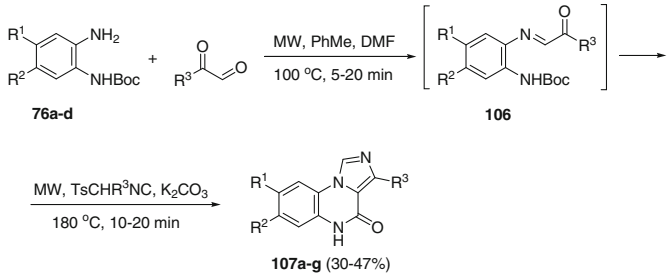
Scheme 4.46 1-(*o*-Methylaminophenyl)imidazole-2,5-dione as precursor for the synthesis of imidazo[1,5-*a*]quinoxalines



Scheme 4.47 Synthesis and recyclization of 4′-methyl-3′,4′-dihydro-1*H*,1′*H*-spiro [pyrimidine-5,2′-quinoxaline]-2,4,6(3*H*)-trione

4.4 Other Methods of Synthesis of Imidazo[1,5-*a*] Quinoxalines

Three-component condensation of *N*-Boc-1,2-DABs **76**, ethyl glyoxylate and substituted tosyl isocyanates in the presence of potassium carbonate on heating and under microwave irradiation (the Van Leusen strategy mentioned above) has been described (DeMoliner and Hulme 2012b). The reaction proceeds as a one-pot process, but in two stages; cyclization of intermediates **106** leads to imidazo[1,5-*a*] quinoxalin-4-ones **107a–g** (Scheme 4.48).



107 $R^1 = R^2 = H$ (**a**,**b**): $R^3 = H$ (**a**), Et (**b**); $R^1 = R^2 = R^3 = Me$ (**c**); $R^2 = R^3 = H$ (**d**,**f**): $R^1 = F$ (**d**), OMe (**f**); $R^2 = H$, $R^1 = F$, $R^3 = Et$ (**e**); $R^1 = OMe$, $R^2 = H$, $R^3 = Me$ (**g**)

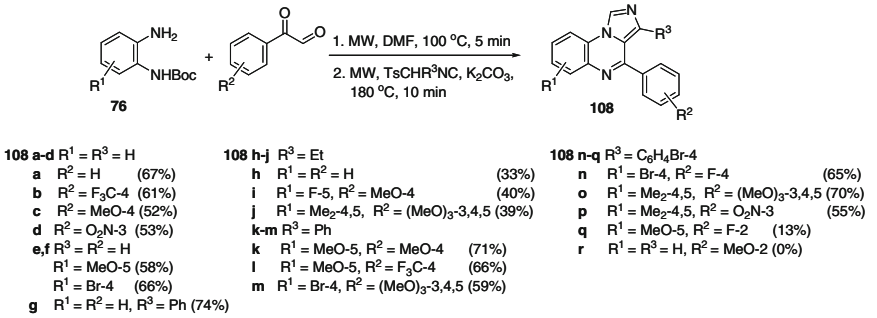
Scheme 4.48 Three-component condensation of *N*-Boc-*o*-diaminobenzenes, ethyl glyoxylate and substituted tosyl isocyanates for the synthesis imidazo[1,5-*a*]quinoxalin-4-ones

The use of phenyl-substituted glyoxals rather than ethyl glyoxylate under analogous conditions leads to 4-arylimidazo[1,5-*a*]quinoxalines **108** (Scheme 4.49) (DeMoliner and Hulme 2012a).

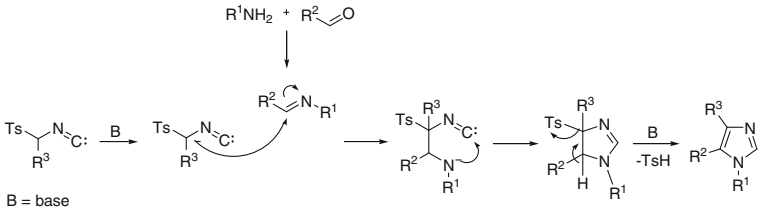
This method enables the introduction of diverse substituents into the heterocycle, no matter whether they have electron-donating or electron-withdrawing properties. The only limitation found by the authors is related to the use of 2-substituted phenylglyoxaldehydes. In this case, the yield of the product is considerably reduced (imidazoquinoxaline **108q**) or the product does not form (the synthesis of compound **108r** was unsuccessful). This is caused by the extreme sensitivity of the reaction to steric factors. Variation of the substituent in isocyanide also has an effect on the yield of the product. In particular, the use of aryl-substituted *p*-tosylmethyl *iso*-cyanides (R^3 = Ar) leads to an increase in the yield of compounds **108g**, **k**, **o**. At the same time, ethyl-substituted *p*-tosylmethyl *iso*-cyanides (R^3 = Et) give products **108h–j** in considerably lower yields.

Formation of the imidazole ring in this case is shown in Scheme 4.50. It involves the formation of Schiff bases in the reaction of amine with aldehyde with subsequent cyclization initiated by tosylmethyl isocyanide (Van Leusen and Van Leusen 2012).

Closure of bonds in synthesis of imidazoquinoxalines **108**, according to the fragmental approach used by us, is shown in Fig. 4.5.



Scheme 4.49 Three-component condensation of *N*-Boc-1,2-DABs, 2-oxo-2-phenylacetaldehydes and substituted tosyl isocyanates for the synthesis imidazo[1,5-*a*]quinoxalin-4-ones



Scheme 4.50 Plausible mechanism for the formation of imidazole ring

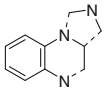


Fig. 4.5 Scheme of formation of the imidazo[1,5-*a*]quinoxaline system in synthesis of compounds **108**

4.5 Synthesis of Imidazo[1,2-*a*]quinoxalines Based on Quinoxaline Derivatives

Among possible variants of assembly of imidazo[1,2-*a*]quinoxalines shown in Fig. 4.6, the following methods are known: methods based on intramolecular cyclization with formation of the N(10)–C(1) and C(2)–N(3) bonds (variants $\mathbf{A1_Q}$, $\mathbf{A3_Q}$), on intermolecular condensation of quinoxaline derivatives with formation of the C(2)–N(3) and N(3)–C(3a) bonds (variant $\mathbf{B3_Q}$) and the N(10)–C(1) and C(2)–N(3) bonds (variant $\mathbf{C1_Q}$), as well as on the processes that occur in the three-component system involving the formation of the N(10)–C(1), C(1)–C(2) and C(2)–N(3) bonds (variant $\mathbf{E1_Q}$).

4.5.1 Methods of Formation of the N(10)–C(1) Bond (Variant $A1_Q$)

Variant $\mathbf{A1_Q}$ of synthesis of imidazo[1,2-*a*]quinoxalines can be exemplified by the rearrangement of 2-(aziridino)quinoxaline derivatives **109a**, **b** by the Gabriel–Heine reaction (Heine 1962). This method has been used to synthesize, for the first time, dihydroimidazo[1,2-*a*]quinoxalines **110a**, **b** (Scheme 4.51) (Heine and Brooker

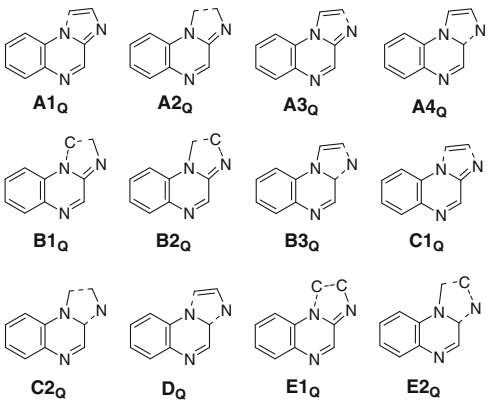
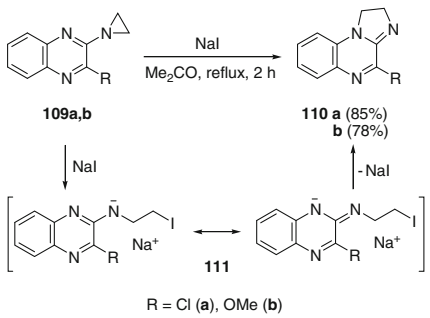
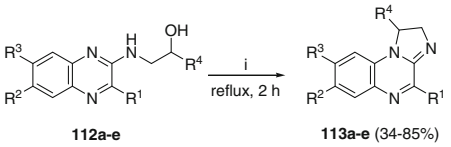


Fig. 4.6 Possible variants of construction of the imidazo[1,2-*a*]quinoxaline system on the basis of quinoxaline derivatives



Scheme 4.51 The Gabriel–Heine reaction 2-(aziridin-1-yl)quinoxalines for the synthesis of imidazo[1,2-*a*]quinoxalines



Scheme 4.52 Cyclization of 2-(2-hydroxyethylamino) quinoxalines for the synthesis of imidazo[1,2-*a*]quinoxalines

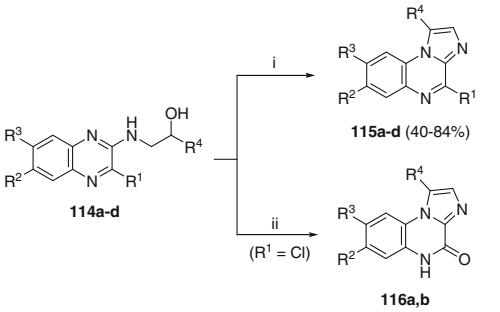
1962). The method consists in the opening of the aziridine ring and closure of the imidazole ring in intermediate compounds **111**.

2-(2-Hydroxyethylamino)quinoxalines **112a–e** are cyclized into 1,2-dihydroimidazo[1,2-*a*]quinoxalines **113a–e** under the action of dehydrating agents, such as thionyl chloride, HCl or phosphorus(V) oxochloride (Scheme 4.52) (Hirotaka et al. 1970; Ohmori et al. 1997; Borchardt et al. 2010, 2011b).

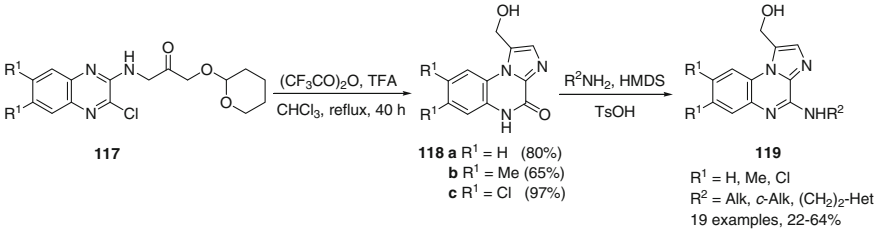
Intramolecular cyclocondensation of 1-[(quinoxalin-2-yl)amino]alkan-2-ones **114a–d** in the presence of trifluoroacetic anhydride leads to formation of aromatic imidazoquinoxalines **115a–d** (Ohmori et al. 1997; Parra et al. 2001; Deleuze-Masquefa et al. 2004, 2010). At the same time, cyclization of chloro derivatives **114a**, **b** in boiling xylene in the presence of TsOH leads to imidazo[1,2-*a*]quinoxalin-4(5*H*)-ones **116a**, **b** (Scheme 4.53) (Deleuze-Masquefa et al. 2004).

Boiling compounds **117** with trifluoroacetic anhydride and trifluoroacetic acid leads to formation of 1-hydroxymethylimidazo[1,2-*a*]quinoxalin-4(5*H*)-ones **118a–c**, the products of cyclization and hydrolysis. These derivatives react with primary amines in the presence of hexamethyldisilazane (HMDS) and TsOH at room temperature to form corresponding 4-amino derivatives **119** (Scheme 4.54) (Liu et al. 2004).

2-(2,2-Dialkoxyethylmino)quinoxalines **120** with R^3 = H, Cl, N $(CH_2CH_2)_2NBoc$ are cyclized under the action of HCl or TsOH to form imidazo [1,2-*a*]quinoxalines **121** (McQuaid et al. 1992; Albaugh and Hutchison 1993, 1995; Borchardt et al. 2010; Kim et al. 2011). The oxidation of compound **121**



Scheme 4.53 Intramolecular cyclocondensation of 1-[(quinoxalin-2-yl)amino]alkan-2-ones in the presence of trifluoroacetic anhydride and in the presence of TsOH



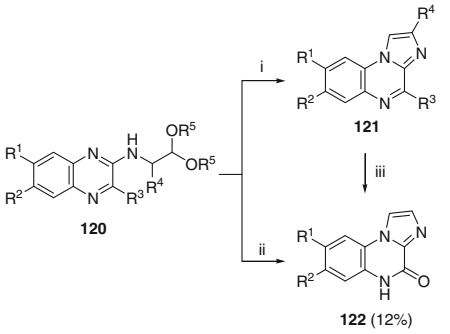
Scheme 4.54 Synthesis and amidation of 1-hydroxymethylimidazo[1,2-*a*]quinoxalin-4(5*H*)-ones with primary amines

(R^1 = R^2 = Cl, R^3 = R^4 = H) by magnesium monoperoxyphthalate leads to corresponding imidazo[1,2-*a*]quinoxalin-4(5*H*)-one **122** (R^1 = R^2 = Cl) (McQuaid et al. 1992).

Imidazoquinoxalin-4-ones **122** also form when 3-chloroquinoxalines **120** (R^3 = Cl) are treated with 48 % HBr solution (McQuaid et al. 1992) or when quinoxalin-2-ones **120** (R^3 = OH) are heated for a long time in hydrochloric acid (Scheme 4.55) (Albaugh and Hutchison 1993, 1995).

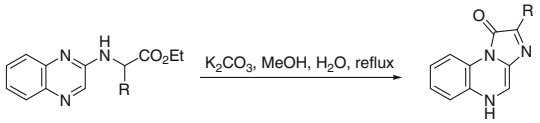
Annulation of the imidazole ring is a result of intramolecular condensation involving the imine nitrogen atom of the quinoxaline system and the carbon atom of not only the alkyl halide, ketone and aldehyde groups but also of the ester group and acetylene moiety. In particular, the condensation of ethyl esters of α-substituted *N*-(quinoxalin-2-yl)glycines **123a–j** in aqueous methanol in the presence of potassium carbonate leads to imidazoquinoxalinones **124a–j** (Scheme 4.56) (Albaugh and Hutchison 1993, 1995).

Scheme 4.55 Cyclization of 2-(2,2-dialkoxyethylamino) quinoxalines under two different conditions



R^1 = H, F, Cl; R^2 = H, F, Cl, CF_3; R^3 = H, Cl, OH, $N(CH_2CH_2)_2NBoc$;
R^4 = H, C_6H_4X (X = H, F-2, F-3, F-4, Cl-3, Cl-4, Me-4, MeO-3, EtO-4), Th-2, methyl-5-thiophen-2-yl; R^5 = Me, Et
i = HCl or TsOH, reflux (for R^3 = H, Cl, $N(CH_2CH_2)_2NBoc$)
ii = 48% HBr, reflux, 4 h or HCl, reflux, 24 h (for R^3 = Cl, OH)
iii = $Mg(O_2CC_6H_4CO_3H\text{-}4)_2$, 55 °C, 18 h (for R^1 = R^2 = Cl, R^3 = R^4 = H)

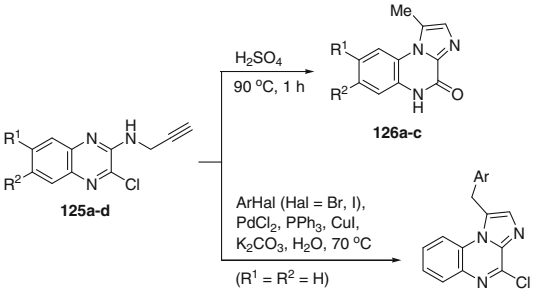
Scheme 4.56 Cyclization of α-substituted *N*-(quinoxalin-2-yl)glycines



R = Ph (**a**), Th-2 (**b**), methyl-5-thiophen-2-yl (**c**), C_6H_4X [X = MeO-3 (**d**), EtO-4 (**e**), F-3 (**f**), F-4 (**g**), Cl-3 (**h**), Cl-4 (**i**), Me-4 (**j**)]

3-Chloroquinoxalines **125a**, **b** with the propargylamino group in the 2-position are cyclized under the action of concentrated sulfuric acid into imidazoquinoxalines **126a**, **b** (Ceccarelli et al. 1998), accompanied by hydrolysis and elimination of the chlorine atom. Analogously, benzo[*g*]quinoxaline **125c** converts into benzo[*g*]imidazo[1,2-*a*]quinoxaline **126c** in 30 % yield (Scheme 4.57) (Beaulieu et al. 2007).

Scheme 4.57 Cyclization of 3-chloro-*N*-(prop-2-ynyl) quinoxalin-2-amines under two different conditions



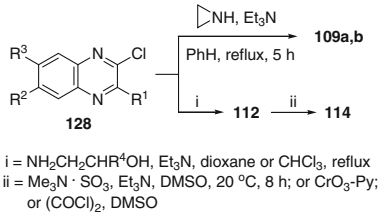
125 R^2 = Cl (**a**,**b**): R^1 = H (**a**), Cl (**b**); R^1-R^2 = benzo (**c**); R^1 = R^2 = H (**d**);
126 R^2 = Cl (**a**,**b**): R^1 = H (**a**), Cl (**b**); R^1-R^2 = benzo (**c**);
127 Ar = $C_6H_{5\text{-}n}X_n$ [X_n = O_2N-2 (**a**), O_2N-4 (**b**), O_2N-2-Cl-4 (**c**), O_2N-4-Cl-2 (**d**), Ac-4 (**e**), OHC-2 (**f**), NC-4 (**g**)]

The use of the palladium–copper catalyst enables the cyclization of compound **125d** under milder conditions, which leads to the retention of the chlorine atom in the molecule. Owing to the presence of aryl iodides (bromides) in the reaction mixture, quinoxaline **125d** converts into 1-benzyl-substituted imidazo[1,2-*a*]quinoxalines **127a–g** in one-pot process. The use of iodine analogs instead of bromonitrobenzenes allows one to increase the yield of compounds **127a**, **b** by 20 % (Bakherad et al. 2012).

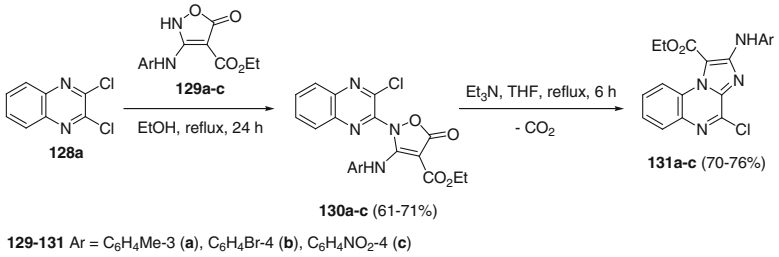
It is likely that ring closure in these reactions occurs through the intermediate formation of the corresponding acetonylamino derivatives of quinoxalin-2(1*H*)-one and benzo[*g*]quinoxalin-2(1*H*)-one.

Precursors of imidazoquinoxalines–compounds **109a**, **b** and **112**–have been synthesized from chloroquinoxalines **128** and corresponding amines in the presence of Et_3N. To oxidize aminoalcohols **112** to ketones **114**, different oxidative systems have been used: a complex of trimethylamine and sulfuric anhydride in DMSO, chromium(VI) oxide in pyridine (Sarett method) (Luzzio 1998; Caamano et al. 2000), and dichloroxalate in DMSO (Swern method) (Scheme 4.58) (Ohmori et al. 1997; Parra et al. 2001; Deleuze-Masquéfa et al. 2004).

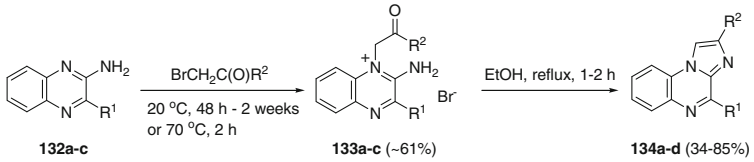
The reaction of 2,3-dichloroquinoxaline **128a** with arylaminoisoxazolones **129a–c** gives oxazolylquinoxalines **130a–c**, which rearrange on heating in THF in the presence of triethylamine into imidazoquinoxalines **131a–c** with elimination of CO_2 (Scheme 4.59) (Poursattar et al. 2012).



Scheme 4.58 Synthesis of precursors of imidazoquinoxalines



Scheme 4.59 Synthesis and cyclization of oxazolylquinoxalines



132 R^1 = NHMe (**a**), NHEt (**b**), Cl (**c**)
133 R^2 = CO_2Et (**a,b**): R^1 = NHMe (**a**), NHEt (**b**); R^1 = Cl, R^2 = H (**c**)
134 R^2 = CO_2Et (**a-d**): R^1 = NHMe (**a**), NHEt (**b**), OH (**d**); R^1 = Cl, R^2 = H (**c**)

Scheme 4.60 Synthesis and cyclization of salts of 2-aminoquinoxalines with bromoacetaldehyde and ethyl bromopyruvate

4.5.2 Method of Formation of the C(2)–N(3) Bond (Variant A3$_Q$)

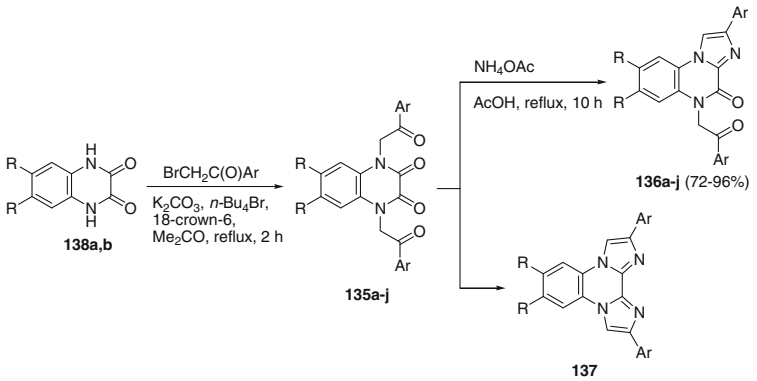
The reaction of 2-aminoquinoxalines **132a–c** with bromoacetaldehyde and ethyl bromopyruvate gives salts **133a–c**, which undergo intramolecular cyclization on heating in ethanol to give imidazoquinoxalines **134a–d** (Scheme 4.60) (Ramm and Barnes 1980; Ager et al. 1988; Parra et al. 2001).

4.5.3 Method of Formation of the C(2)–N(3) and N(3)–C(3a) Bonds (Variant B3$_Q$)

Heating 1,4-bis(aroylmethyl)quinoxalin-2,3-diones **135a–j** in acetic acid in the presence of ammonium acetate leads to 2-aryl-5-aroylmethylimidazo[1,2-*a*] quinoxaline-4-ones **136a–j** (**B3$_Q$**-type cyclization, see Fig. 4.6), whereas expected 1,5-diarylbis(imidazo[1,2-*a*:2′,1′-*c*])quinoxalines **137** are not identified in the reaction mixture. Starting compounds **135** have been obtained by alkylation of quinoxalinediones **138a**, **b** with aroylmethyl bromides (Scheme 4.61) (Hariharakrishnan et al. 2008).

4.5.4 Methods of Formation the N(10)–C(1) and C(2)–N(3) Bonds (Variant C1$_Q$)

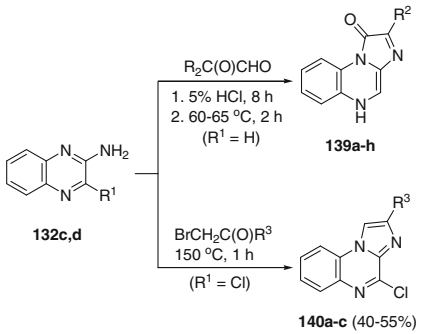
Imidazoquinoxalines can be synthesized from aminoquinoxalines **132** and bromoketones or ketoaldehydes without isolation of corresponding quaternized derivatives **133** (see Scheme 4.60). This method was used to synthesize compounds **139a–h** from 2-aminoquinoxaline **132d** and compounds **140a–c** from 3-chloro



135, 136 R = H (**a-e**): Ar = Ph (**a**), C_6H_4OMe-4 (**b**), C_6H_4Br-4 (**c**), C_6H_4Cl-4 (**d**), C_6H_4F-4(**e**); R = NO_2 (**f-j**): Ar = Ph (**f**), C_6H_4OMe-4 (**g**), C_6H_4Br-4 (**h**), C_6H_4Cl-4 (**i**), C_6H_4F-4 (**j**)

Scheme 4.61 Synthesis and cyclization of 1,4-bis(aroylmethyl)quinoxalin-2,3-diones

Scheme 4.62 Cyclization of aminoquinoxalines under two different conditions



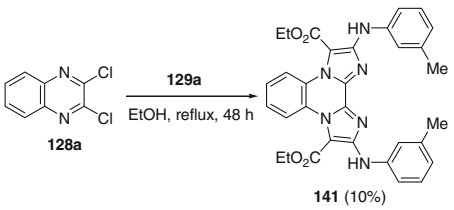
132 R^1 = Cl (**c**), H (**d**)
139 R^2 = Me (**a**), $C_6H_3(OMe)_2$-3,4 (**b**), $C_6H_3F_2$-2,4 (**c**), $C_6H_3F_2$-2,6 (**d**), C_6H_4OEt-3 (**e**), C_6H_4Et-3 (**f**), C_6H_3F-3-OMe-4 (**g**), F_3C (**h**)
140 R^3 = Ph (**a**), C_6H_4OMe-4 (**b**), Th-2(**c**)

derivative **132c** (Scheme 4.62) (Catarzi et al. 1994; Albaugh and Hutchison 1995; Teranishi 2007).

4.5.5 Method of Formation of the N(10)–C(1) and N(3)–C(3a) Bond (Variant D_Q)

Refluxing 2,3-dichloroquinoxaline **128a** with two equivalents of arylaminoisoxazolone **129a** in ethanol for 48 h in the absence of bases (see Sect. 4.5.1) leads to bis(imidazo)quinoxaline system **141** (Scheme 4.63) (Poursattar et al. 2012).

Scheme 4.63 Reaction of 2,3-dichloroquinoxaline with two equivalents of arylaminoisoxazolone

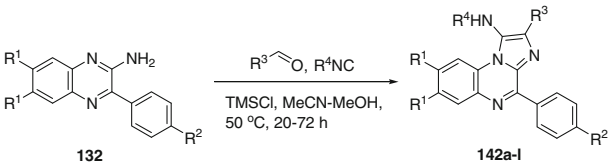


4.5.6 *Method of Formation of the N(10)–C(1), C(1)–C(2) and C(2)–N(3) Bonds (Variant E1$_Q$)*

The multicomponent reaction of 2-amino-3-arylquinoxalines **132** with aldehydes and isocyanides under the conditions of the Groebke–Blackburn–Bienaymé reaction (Blackburn et al. 1998; Groebke et al. 1998; Ivachtchenko et al. 2010) leading to 1-aminoimidazo[1,2-*a*]quinoxalines **142a–l** is an example of synthesis of such compounds according to variant **E1$_Q$** (Table 4.3) (Krasavin and Parchinsky 2008; Krasavin et al. 2009).

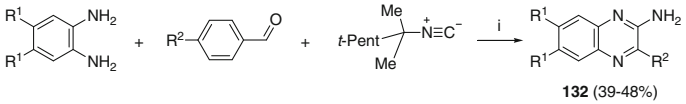
It should be noted that starting 2-aminoquinoxalines **132** for this reaction have also been obtained in a multicomponent system by the modified Groebke–Blackburn–Bienaymé reaction, using 1,2-DABs as one of the reactants (Scheme 4.64).

Table 4.3 The Groebke–Blackburn–Bienaymé reaction in the 1-aminoimidazo[1,2-*a*]quinoxalines synthesis



TMS =Trimethylsilyl

142	R^1	R^2	R^3	R^4	Time (h)	Yield (%)
142a	H	H	C_6H_4F-4	$(CH_2)_3OPr$-*i*	20	65
142b	H	H	*n*-Pr	$CH_2C_6H_4OMe$-4	48	45
142c	H	H	C_6H_4OBu-*n*-4	$(CH_2)_2Pr$-*i*	48	52
142d	H	H	$C_6H_2(OMe)_3$-3,4,5	$CH_2C_6H_4OMe$-4	72	68
142e	Me	H	Py-3	$EtO(CH_2)_3$	20	73
142f	Me	H	C_6H_4OPr-*i*-4	EtO_2CCH_2	48	56
142g	Me	H	methyl-1-imidazol-3-yl	*c*-C_5H_9	72	34
142h	Me	H	C_6H_4CN-4	*t*-Bu	20	72
142i	Me	CO_2Me	*n*-Pr	*t*-Bu	48	64
142j	Me	H	*n*-Pr	*t*-Bu	48	71
142k	Me	H	dimethyl-1,3-imidazol-4-yl	$(CH_2)_3OEt$	72	49
142l	H	Ph	Ph	*c*-C_7H_{13}	—	33



i = 1. HCl, MeOH, 8 h; 2. DDQ, 20 °C, 3 h
DDQ = 2,3- Dichloro-5,6-dicyano-1,4-benzoquinone

Scheme 4.64 The Groebke–Blackburn–Bienaymé reaction in the 2-aminoquinoxalines synthesis

4.6 Synthesis of Imidazo[1,2-*a*]quinoxalines on the Basis of Imidazole Derivatives

The known variants of assembly of the imidazo[1,2-*a*]quinoxaline system from imidazoles involve different intramolecular cyclizations of imidazole derivatives accompanied by the formation of the C(3a)–C(4), C(4)–N(5) and C(9a)–N(10) bonds (variants $\mathbf{A1_I}$, $\mathbf{A2_I}$ and $\mathbf{A4_I}$, respectively), as well as intermolecular cyclizations of imidazole derivatives with different equivalents of monoatomic carbon synthons accompanied by the formation of the C(3a)–C(4) and C(4)–N(5) bonds (variant $\mathbf{B1_I}$) and with equivalents of triatomic nitrogen–carbon synthons accompanied by the formation of the C(4)–N(5) and C(9a)–N(10) bonds (variant $\mathbf{D1_I}$) (Fig. 4.7).

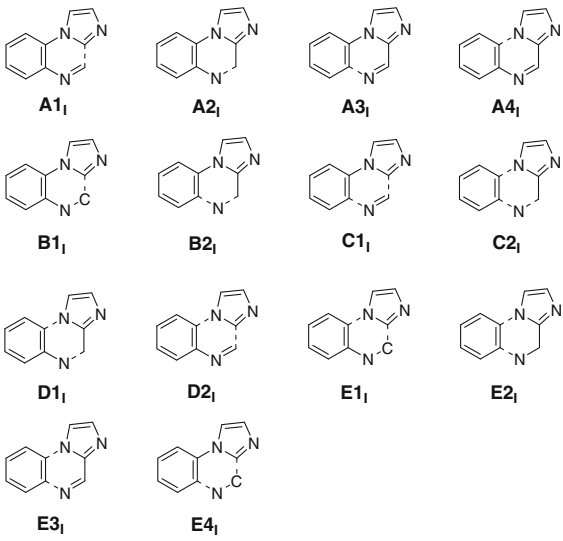


Fig. 4.7 Possible variants of construction of the imidazo[1,2-*a*]quinoxaline system on the basis of imidazoles

4.6.1 Method of Formation of the C(3a)–C(4) Bond (Variant $A1_I$)

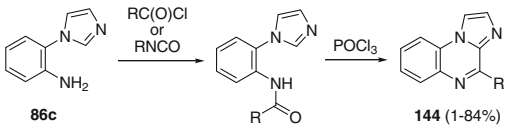
One of the key methods of synthesis of imidazo[1,2-*a*]quinoxalines on the basis of imidazoles is $\mathbf{A1_I}$-type synthesis. In this case, imidazole ring annulation is a result of formation of the C(3a)–C(4) bond. In particular, 1-(2-acylaminophenyl)- or 1-(2-amino-carbonylaminophenyl)imidazoles **143**, obtained by the reaction of *N*-(2-aminophenyl)imidazole **86c** and acetyl chlorides or isocyanates, are converted under the action of phosphorus(V) oxochloride into 4-substituted imidazoquinoxalines **144** (Warner and Luber 1979a, b, c, 1980a, b, c, d, e; Lamberth 1999; Chen et al. 2002b). More than 100 imidazo[1,2-*a*]quinoxalines have been synthesized by this method (Scheme 4.65).

4.6.2 Methods of Formation of the C(4)–N(5) Bond (Variant $A2_I$)

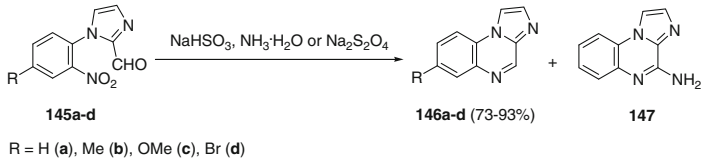
The reduction of 1-(2-nitrophenyl)-2-formylimidazoles **145b–d** by sodium hydrosulfite in an aqueous ammonia leads to imidazo[1,2-*a*]quinoxalines **146b–d** in high yields (Simonov et al. 1971; Uryukina et al. 1972). It is likely that the products are generated through the $\mathbf{A2_I}$-type intramolecular cyclization of the corresponding amino derivatives. In the case of compound **145a**, 4-aminoimidazo[1,2-*a*]quinoxaline **147** was isolated in 3 % yield as a side product (Simonov et al. 1972). However, the reduction of compound **145a** by sodium dithionite leads only to imidazo[1,2-*a*]quinoxaline **146a** in 50 % yield (Scheme 4.66) (Simonov et al. 1971).

The reduction of nitro ester **148** by iron powder in aqueous ethanolic acetic acid under ultrasonic activation for 4 h is accompanied by intramolecular cyclization to give imidazoquinoxalin-4-one **149** in good yield (Scheme 4.67) (Li et al. 2013).

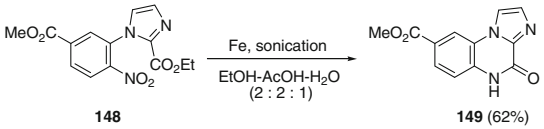
It is known that the appropriately arranged methyl group in one ring and the nitro group in the other ring react with each other in the presence of ferrous oxalate to form an extra central ring (Scott and Söberberg 2002). According to this methodology, 2-methyl-1-(2-nitrophenyl)-imidazoles **150a**, **e** in the presence of



Scheme 4.65 Synthesis and cyclization of 1-(2-acylaminophenyl)- or 1-(2-aminocarbonylaminophenyl)imidazoles

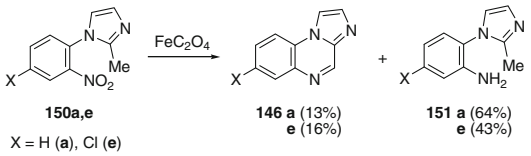


Scheme 4.66 Cyclization of 1-(2-nitrophenyl)-2-formylimidazoles when exposed to sodium hydrosulfite in an aqueous ammonia



Scheme 4.67 Cyclization of 1-(2-nitrophenyl)-2-ethoxycarbonylimidazoles when exposed to iron powder in aqueous ethanolic acetic acid

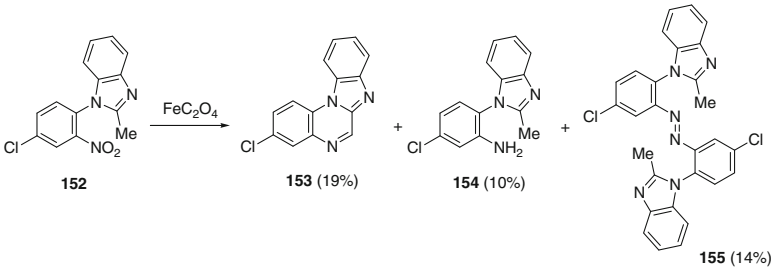
Scheme 4.68 Cyclization of 1-(2-nitrophenyl)-2-methylimidazoles when exposed to iron oxalate



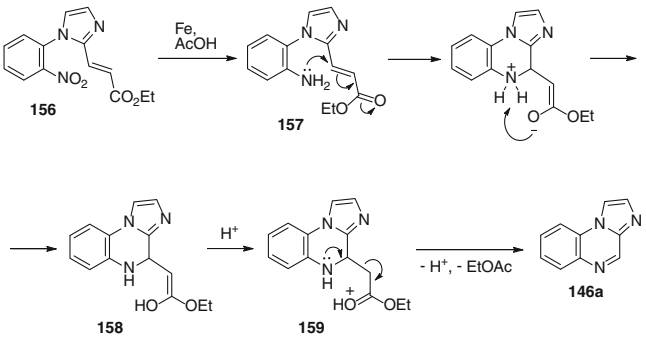
iron oxalate are transformed into imidazo[1,2-*a*]quinoxalines **146a**, **e** (Scheme 4.68) (Bacon and Hamilton 1974). However, the cyclization competes with the reduction of the nitro group to the amino group to give compounds **151a**, **e**.

Benzannulated analogue **152** gives, under these conditions, a mixture of benzimidazoquinoxaline **153**, primary amine **154** and azo compound **155** in 19, 10, and 14 % yields, respectively (Scheme 4.69) (Bacon and Hamilton 1974).

The presence of the ethoxycarbonylvinyl moiety in the 2-position of the imidazole ring spatially close to the nitro group of compound **156** facilitates



Scheme 4.69 Cyclization of 1-(4-chloro-2-nitrophenyl)-2-methylbenzoimidazole when exposed to iron oxalate

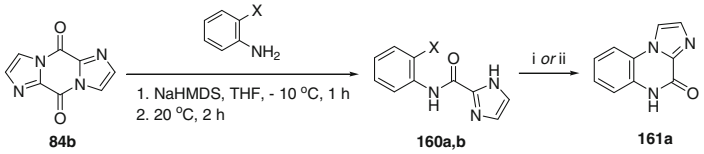


Scheme 4.70 Cyclization of (*E*)-ethyl 3-(1-(2-nitrophenyl)-1*H*-imidazol-2-yl)acrylate when exposed to iron in acetic acid

intramolecular cyclization. It occurs through the Michael nucleophilic addition of the amino group generated by the reduction of the NO_2 group. This reaction leads to annulation of the pyrazine ring in intermediate **157** to give tricycle **158**. The elimination of ethyl acetate from cation **159** contributes to the formation of unsubstituted imidazo[1,2-*a*]quinoxaline **146a** (Scheme 4.70) (Mishra and Batra 2010).

4.6.3 Methods of Formation of the C(9a)–N(10) Bond (Variant A4$_I$)

A4$_I$-type methods of synthesis are common for imidazo[1,5-*a*]- and imidazo[1,2-*a*] quinoxalines. When kept in boiling dimethylacetamide in the presence of NaH for 6 h, anilide **160a** converts into imidazo[1,2-*a*] quinoxalin-4-one **161a** in 80 % yield (Scheme 4.71, conditions *i*) (Deleuze-Masquéfa et al. 2009c, 2010). It has been shown that a combination of pyrrole-2-carbohydrazide attached to a polystyrene substrate (PSP) with CuI is a regenerable heterogeneous catalytic system for Ullmann C–N coupling in an aqueous medium. It allows one to aminate functionalized haloarenes with anilines, benzylamines, aliphatic amines, and even imidazole. In the last case, compound **160b** can be converted into imidazo[1,2-*a*] quinoxalin-4-one **161a** via an alternative route without using air-sensitive NaH and an organic solvent, DMA. The reaction proceeds in water, which makes the process much more effective and environmentally safe (conditions *ii* in Scheme 4.71, Huang et al. 2013b). Initial anilides **160** have been synthesized by acylation of *o*-haloanilines with diimidazo[1,2-*a*;1′,2′-*d*]pyrazine-5,10-dione **84b**.

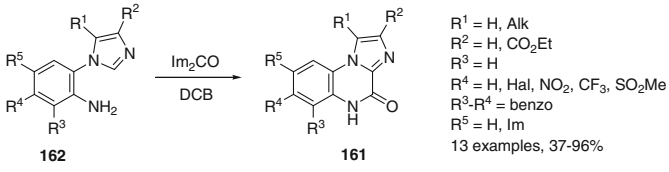


Scheme 4.71 Synthesis and cyclization of *N*-(2-fluorophenyl)- and *N*-(2-iodophenyl)-1*H*-imidazole-2-carboxamides

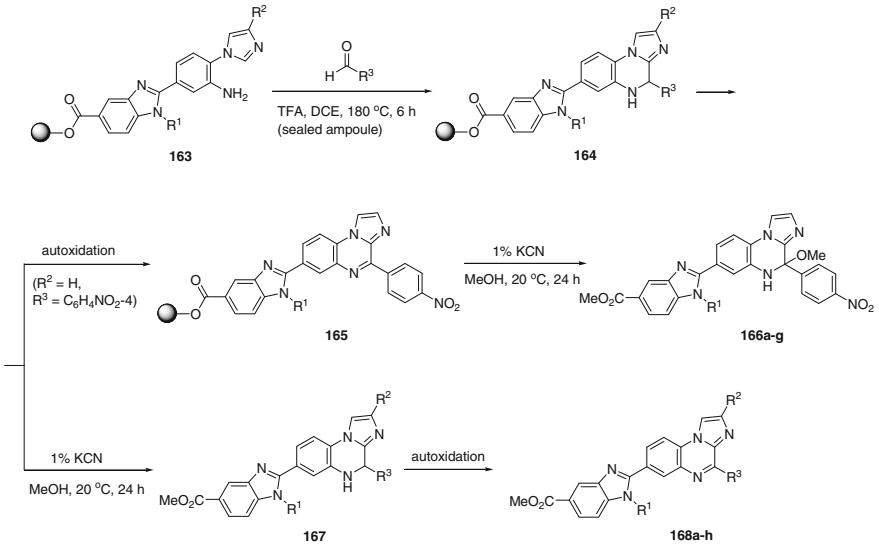
4.6.4 Methods of Formation of the C(3a)–C(4) and C(4)–N(5) Bonds (Variant B1$_I$)

The reaction of 1-(2-aminophenyl)imidazoles **162** with carbonyldiimidazole on heating in dichlorobenzene leads to imidazoquinoxalin-4-ones **161** (Scheme 4.72) (Davey et al. 1991; Colotta et al. 1995; Jeppesen 1995; Treiber et al. 1996, 1997; Ohmori et al. 1997; Campiani et al. 1999; Chen et al. 2002a, 2011). The yields vary from moderate to high.

The Pictet–Spengler reaction (Jiang et al. 2002; Tsuji et al. 2003) of compounds **163**, with the unsubstituted 2-position in the imidazole ring, and aldehydes yields imidazo[1,2-*a*]quinoxaline **164** (Chen et al. 2011). The reaction is carried in the solid phase. Compounds **163** are synthesized in four stages from an *o*-phenylenediamine derivative attached to a polymeric support through an ester group in the 5-position of the benzimidazol-2-yl moiety (Chen et al. 2011). In the case of electron-withdrawing substituents in the 4-position of the benzene ring of substituent R^3 and in the absence of a substituent in the 2-position of imidazoquinoxalines **164** (R^2 = H, R^3 = $C_6H_4NO_2$-4), autoxidation occurs to form compounds **165**. The product is removed from the polymer support with a 1 % potassium cyanide solution in methanol at room temperature. Compounds **165** add methanol at the C=N bond, which is favored by the presence of an electron-withdrawing substituent, to form compounds **166a–g**. Under the same conditions, compounds **164** are first converted into dihydroimidazoquinoxalines **167**, which are oxidized to products **168a–h** (Scheme 4.73).



Scheme 4.72 Cyclization of 1-(2-aminophenyl)imidazoles when exposed to carbonyldiimidazole



163 **164** **165** **166a-g** **167** **168a-h**

166 R^1 = *i*-Pr (**a**, 60%), *i*-C_5H_{11} (**b**, 70%), *c*-C_6H_{11} (**c**, 73%), *c*-C_8H_{15} (**d**, 62%), $(CH_2)_3OMe$ (**e**, 67%), 2-(cyclohexen-1-yl))ethyl (**f**, 79%), 2-(tetrahydrofuran-2-yl)ethyl (**g**, 70%)

168 R^1 = 2-(cyclohexen-1-yl)ethyl: R^2 = H, R^3 = Ph (**a**, 70%); R^2 = H, R^3 = C_6H_4OMe-4 (**b**, 82%); R^2 = H, R^3 = *n*-Pr (**c**, 65%); R^2 = Me, R^3 = Ph (**d**, 58%); R^2 = Me, R^3 = C_6H_4OMe-4 (**e**, 67%); R^2 = Me, R^3 = *n*-C_6H_{13} (**f**, 56%); R^2 = Me, R^3 = 4-$O_2NC_6H_4$ (**g**, 69%); R^1 = Bu^n, R^2 = Me, R^3 = 4-$O_2NC_6H_4$ (**h**, 65%)

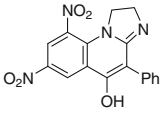
DCE = Dichloroethane

Scheme 4.73 Cyclization of 1-(2-aminophenyl)imidazole derivatives in the solid phase and some transformations of the obtained products

4.6.5 Methods of Formation of the C(4)–N(5) and C(9a)–N(10) Bonds (Variant D1$_I$)

The reaction of 1,3-dinitro-4-fluorobenzene **169a** with cyclic amidine **170a** (tolazoline) yields imidazo[1,2-*a*]quinoxaline *N*-oxide **171a**. The reactions of compounds **169b**–**h** with imidazoles **170a**–**f**, are analogous and yield corresponding imidazo[1,2-*a*]quinoxaline *N*-oxides **171b**–**p** (Scheme 4.74) (Strauss et al. 1978; Parthasarathy et al. 1983; Ellames and Jaxa-Chamiec 1987).

It should be noted that the same reaction of isomer **169i** (rather than **169h**), which contains the ethoxycarbonyl group in the *ortho*-position to the chlorine atom, on refluxing in EtOH for 5 min leads to imidazoquinoline **172**–a carbon analogue of imidazo[1,2-*a*]quinoxaline (Strauss et al. 1978).



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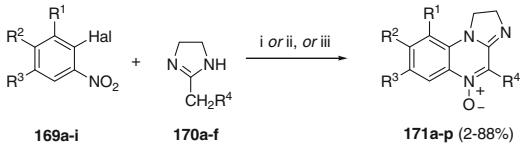
The condensation of *o*-iodoaniline with 2-formylimidazole in the presence of a copper catalyst results in imidazo[1,2-*a*]quinoxaline **146a**. An analogous

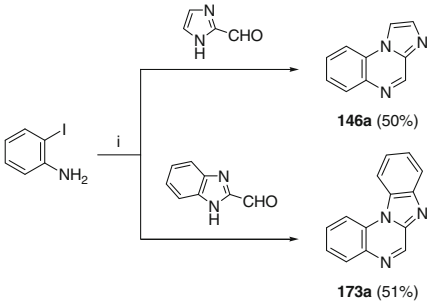


169a-i **170a-f** **171a-p** (2-88%)

169 Hal = F, $R^1 = R^2 = H$ (**a-d**): $R^3 = NO_2$ (**a**), H (**b**), Bz (**c**), 4-methyl-2- ethylaminothiazol-5-yl (**d**);
Hal = F, $R^1 = R^3 = H$ (**e,f**): R^2 = F (**e**), Cl (**f**); Hal = $R^2 = R^3$ = F, R^1 = H (**g**);
Hal = Cl, R^2 = H (**h,i**): $R^1 = NO_2$, $R^3 = CO_2Et$ (**h**), $R^1 = CO_2Et$, $R^3 = NO_2$ (**i**)
170 R^4 = Ph (**a**), C_6H_4F-4 (**b**), H (**c**), $C_6H_4NH_2$-4 (**d**), $C_6H_3(OMe)_2$-3,4 (**e**), $C_6H_2(OMe)_3$-3,4,5 (**f**)
171 $R^1 = R^3 = NO_2$, R^2 = H, R^4 = Ph (**a**); R^1 =NO2, R^2 = H, $R^3 = CO_2Et$, R^4 = Ph (**b**);
$R^1 = R^2 = R^4$ = H, R^3 = 4-methyl-2-ethylaminothiazol-5-yl (**c**);
$R^1 = R^2 = R^3$ = H (**d-g**): $R^4 = C_6H_4F$-4 (**d**), $C_6H_4NH_2$-4 (**e**), $C_6H_3(OMe)_2$-3,4 (**f**), $C_6H_3(OMe)_2$-3,4,5 (**g**);
$R^1 = R^2$ = H, $R^3 = NO_2$ (**h-j**): $R^4 = C_6H_4F$-4 (**h**), C_6H_4OMe-4 (**i**), $C_6H_3(OMe)_2$-3,4 (**j**);
$R^1 = R^2$ = H, R^3 = Bz (**k-m**): $R^4 = C_6H_4OMe$-4 (**k**), $C_6H_3(OMe)_2$-3,4 (**l**), Ph (**m**);
R^1 = H, R^4 = Ph (**n-p**): R^2 = F, R^3 = H (**n**), R^2 = Cl, R^3 = H (**o**), $R^2 = R^3$ = F (**p**)
i = MeCN, reflux, 8 h; ii = EtOH, 24 h; iii = K_2CO_3, *i*-PrOH, 50 h

Scheme 4.74 Synthesis imidazo[1,2-*a*]quinoxaline *N*-oxides by interaction of 1,3-dinitro-4-fluoro (and chloro)benzenes with cyclic amidines

Scheme 4.75 Condensation of *o*-iodoaniline with 2-formylimidazole and 2-formylbenzimidazole in the presence of a copper catalyst



146a (50%)

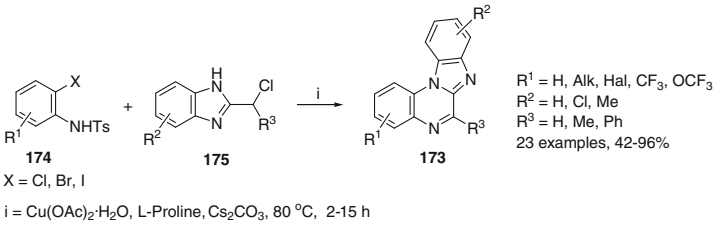
173a (51%)

i = CuI (10 mol%), sparteine (20 mol%), K_3PO_4 (2 equiv), 130 °C, 24 h

reaction with 2-formylbenzimidazole gives benzimidazo[1,2-*a*]quinoxaline **173a** (Scheme 4.75) (Reeves et al. 2010).

There has been developed a convenient and efficient domino process for constructing benz[4,5]imidazo[1,2-*a*]quinoxalines **173** from *N*-tosyl-2-haloanilines **174** and 2-(chloromethyl)-1*H*-benzimidazoles **175** (Scheme 4.76). This reaction proceeds under mild conditions and is catalyzed by copper salts, and the yields vary from moderate to quantitative. Such a Cu-catalyzed one-pot method can be used for synthesis of a large number of compounds with the aim of testing their biological activity.

Studying the effect of the base nature on this process has shown that the use of caesium carbonate affords the target compounds in higher yields as compared with the reactions where K_2CO_3, K_3PO_4, KOH, *t*-BuONa, or *t*-BuOK are used as a base. Six copper-containing catalysts have been tested: $Cu(OAc)_2 \cdot 2H_2O$, CuBr, CuI, CuCl, $CuBr_2$, and $CuCl_2 \cdot 2H_2O$. The best yields have been achieved with $Cu(OAc)_2 \cdot 2H_2O$. In addition, the effects of the solvent and ligand on the reaction efficiency have been studied. The use of DMSO, DMF, dioxane, and toluene leads



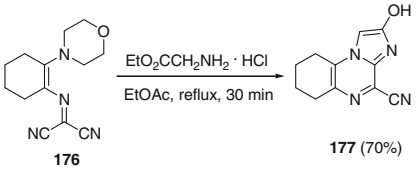
Scheme 4.76 Synthesis of benz[4,5]imidazo[1,2-*a*]quinoxalines from *N*-tosyl-2-haloanilines and 2-(chloromethyl)-1*H*-benzimidazoles

to benzimidazo[1,2-*a*]quinoxaline **173a** in good yield, whereas the reaction is almost absent in THF. The effect of the nature of the halogen atom in initial *N*-tosyl-2-haloanilines **174** on the yields of compounds **173** is as follows: when bromo and iodo derivatives are used, compounds **173** form in rather high yields (78–96 %), while, in the reaction with *N*-tosyl-2-chloroanilines, good yields are achieved only when they contain electron-withdrawing substituent R^1 (otherwise, the yields are <50 %) (Huang et al. 2013a).

4.7 Other Methods of Synthesis of Imidazo[1,2-*a*] quinoxalines

The imidazo[1,2-*a*]quinoxaline system can also be designed on the basis of compounds that contain neither the quinoxaline ring nor the imidazole ring. In particular, the reaction of compound **176** with ethyl glycinate hydrochloride leads to annulation of the imidazopyrazine system and formation of tetrahydroimidazoquinoxaline **177** (Scheme 4.77) (Legroux et al. 1987).

Formation of tricycle **177** is schematically shown in Fig. 4.8.



Scheme 4.77 Cyclization of (2-morpholinocyclohex-1-enyl)carbonimidoyl dicyanide when exposed to ethyl glycinate hydrochloride

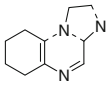


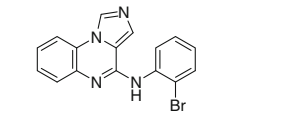
Fig. 4.8 Scheme of formation of the imidazo[1,2-*a*]quinoxaline system in synthesis of compound **177**

4.8 Biological Activity of Imidazo[1,5-*a*]- and Imidazo [1,2-*a*]quinoxalines

Investigation of the biological activity of imidazo[1,5-*a*]- and imidazo[1,2-*a*] quinoxalines began almost simultaneously with the development of methods for their preparation. However, many data were published only in the patent literature. In the late 1980s and in the 1990s, major efforts were made to study the effect of these compounds on the central nervous system. The result of these works was the creation of drugs shown in Fig. 4.1 (Negwer and Scharnow 2001). The range of useful properties of such tricyclic systems has been extended in the last 10–15 years. Below, we present the structures of representatives of this class of compounds grouped by type of biological activity.

4.8.1 Kinase Inhibition

Imidazo[1,5-*a*]quinoxalines **178–180**, containing an arylamine moiety in the 4-position, are inhibitors of the Src-family kinases p56Lck: the 50 % inhibition concentrations (IC_{50}) of these compounds are 170.2, 2.0 and 1.7 nmol L^{-1}, respectively (Chen et al. 2002a, b, c). The presence of an amide group in the 8-position, along with the 4-arylamine substituent, confers to compound **181** the ability to irreversibly inhibit Bruton's tyrosine kinase (BTK) (IC_{50} = 1.93 nmol L^{-1}) (Kim et al. 2011). This compound is used in the treatment of rheumatoid arthritis.



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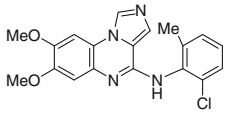
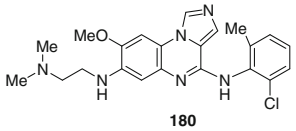


179



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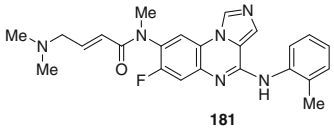
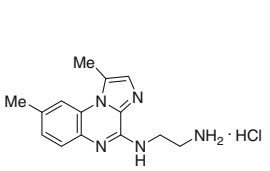
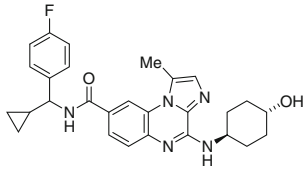


181

Among imidazo[1,2-*a*]quinoxalines, there are a highly efficient IkB-kinase inhibitor–compound **182** (BMS-345541) (Burke et al. 2003)–and a selective inhibitor of JNK1 kinase–compound **183** (AX-13587) (Li et al. 2013).

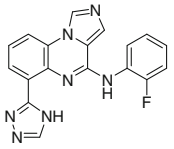


182 (BMS-345541)



183 (AX-13587)

One of the important new areas of biological studies of imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxaline derivatives focuses on their antitumour activity. New potent dual CK2 and PIM kinase inhibitors with the antiproliferative activity against cancer cells have been described (Pierre et al. 2012), for example, compound **184** (IC_{50} = 0.038 (PIM1), 0.043 (PIM2), 0.035 (CK2) mol L^{-1}). 1-Isobutyl-4-methylaminoimidazo[1,2-*a*]quinoxaline (**185**, EAPBO-103), and 1-phenethyl-4-substituted imidazo[1,2-*a*]quinoxalines **186a–c** (EAPBO-201–203) show much higher activity (by a factor of 6–110 and 2–45) against melanoma (A375) than the antitumour drug fotemustine and immunomodulator imiquimod (Moarbess et al. 2008b). Compound **186c** also exhibits higher cytotoxic activity than imiquimod and fotemustine. 4-Methylamino-1-(2-methoxyphenyl)imidazo[1,2-*a*]quinoxaline (**187a**, EAPBO-503) is even more active against melanoma: its activity is 7–9 times higher than that of compound **186c** (Moarbess et al. 2008b; Khier et al. 2010a). The metabolism and pharmacokinetics of these pharmaceuticals have been studied (Khier et al. 2010b; Lafaille et al. 2012). For compound **187a** and its metabolite–1-(2-hydroxyphenyl)-4-methylaminoimidazo[1,2-*a*]quinoxaline (**187b**, EAPBO-603) (Lafaille et al. 2012, 2014)–protocols for the quantification of them in human and rat plasma have been developed (Khier et al. 2009).



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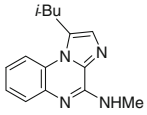
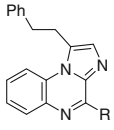
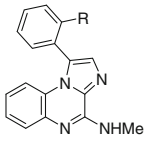


185 (EAPBO-103)



186a-c

R = Cl (**a**, EAPBO-201), NH_2 (**b**, EAPBO-202), NHMe (**c**, EAPBO-203)

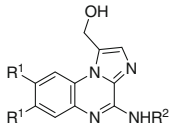


187a,b

R = OMe (**a**, EAPBO-503), OH (**b**, EAPBO-603)

4.8.1.1 Activity Toward the A_1 Adenosine and Histamine Receptors

Currently, study of the effect of the tricyclic compounds under consideration on the central nervous system is continued. 4-Alkylamino-1-hydroxymethylimidazo[1,2-*a*]quinoxalines **188** are A_1 adenosine receptor antagonists, the compound with R^1 = Cl, R^2 is pyrrolidin-1-yl exhibiting the highest activity [inhibition constant (*K*i), 7 nmol L^{-1}] (Liu et al. 2004). It has been stated that the hydroxymethyl group in the 1-position displays the potent affinity toward the binding site of the receptor (Liu et al. 2004).



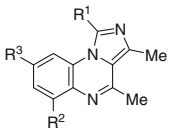
188

R^1 = H, Me, Cl
R^2 = Alk, *c*-Alk, azacycloalkylethyl

Imidazo[1,2-*a*]- and imidazo[1,5-*a*]quinoxalines have been studied as histamine receptor inhibitors (Borchardt et al. 2011a, b).

4.8.2 Phosphodiesterase Inhibition

3,4-Dimethylimidazo[1,5-*a*]quinoxalines **189**, containing different substituents in the 1-, 6- and 8-positions, and above-mentioned imidazo[1,5-*a*]quinoxalines **188** are 10A phosphodiesterase (PDE10A) inhibitors and can be used for designing antischizophrenia drugs (Malamas et al. 2010, 2011b).



189

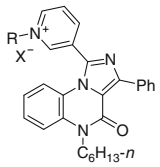
R^1 = Ar, Het
R^2 = H, F, OH, OAlk, fluoroalkoxy
R^3 = H, F, OH, OAlk, fluoroalkoxy, CF_3, morpholin-4-yl

The presence of the pyrrolidine, morpholine, cyclohexane, piperidine, or azacycloheptane moiety in the 1-position of imidazo[1,5-*a*]quinoxalin-4-ones, along with amide groups in the 7(8)-position, leads to inhibition of phosphodiesterase 9 (PDE9); therefore, such compounds are used for developing drugs that eliminate urination disorders (Okada et al. 2009; Kaizawa et al. 2011).

1-Isobutyl-4-methylaminoimidazo[1,5-*a*]quinoxaline **185** exhibits potent inhibitory properties against phosphodiesterase 4 (PDE4) (Deleuze-Masquéfa et al. 2004).

4.8.3 Antimicrobial and Antifungal Activity

Imidazo[1,5-*a*]quinoxalin-4-ones **190a–c** with a quaternized pyridinium substituent in the 1-position have noticeable antimicrobial activity. The antibacterial activity of compounds **190** against *Staphylococcus aureus* is comparable with that of drugs ofloxacin and norfloxacin. In addition, bromide **190b** exhibits fungicidal activity (against *Candida albicans*) comparable with that of drug Amphotericin B, whereas iodide **190c** has no antifungal effect (Kalinin et al. 2013). Both salts show significant antibacterial activity against soil bacterium *Bacillus cereus* (Kalinin et al. 2013).



190a-c

R = Bn, X = Cl (**a**);
R = *n*-C_9H_{19}(**b,c**): X = Br (**b**), I (**c**)

4.9 Conclusions

As can be seen from the material presented in this review, imidazo[1,5-*a*]- and imidazo[1,2-*a*]quinoxalines arouse a great deal of interest of researchers owing to the wide range of biological activity exhibited by them. For this reason, in addition to the improvement of the known methods of their synthesis, an intensive search is carried out for new preparative procedures that afford diverse derivatives.

Analysis of the efficiency of different methods of synthesis of imidazo[1,5-*a*] and imidazo[1,2-*a*]quinoxalines demonstrates that there are currently 26 approaches corresponding to the retrosynthetic analysis of the structure of a heterocyclic system without including the benzene ring. Initial compounds are quinoxaline (see Figs. 4.3 and 4.6) or imidazole derivatives (see Figs. 4.4 and 4.7). For synthesis of imidazo[1,5-*a*]quinoxaline, seven approaches based on quinoxalines and four approaches based on imidazoles have been developed (Table 4.4); for synthesis of imidazo[1,2-*a*]quinoxalines, six approaches based on quinoxalines and five approaches based on imidazoles have been developed (Table 4.5).

These Tables demonstrate which methods of synthesis of imidazo[1,5-*a*] quinoxalines are most widely used, which of them require further development, and which methods remain unused. The formation of imidazo[1,5-*a*]quinoxalines **107** and **108** from compounds **76** and **105**, as well as the formation of imidazo[1,2-*a*]

Table 4.4 Comparison of different approaches to the synthesis of imidazo-[1,5-*a*]quinoxalines (see Figs. 4.3 and 4.4)

Variant	Number of studies	Number of stages	Substituent variation positions	References
$\mathbf{A1_Q}$	7	3–6	1–3	Kollenz (1972), Danswan et al. (1982), Kurasawa et al. (1983), Ager et al. (1988), Mamedov et al. (2002b, 2003, 2004)
$\mathbf{A2_Q}$	1	3	2	Benkovic et al. (1973)
$\mathbf{A3_Q}$	1	3	2	Ahmad et al. (1964)
$\mathbf{B1_Q}$	5	4 or 5	1, 3	Benkovic et al. (1969, 1972), Mamedov et al. (2003), Malamas et al. (2010, 2011a)
$\mathbf{C1_Q}$	6	3–5	1, 3, 5	Mamedov et al. (2002a, 2003), Kalinin and Mamedov (2008a, b), Wang et al. (2012), Kalinin et al. (2013)
$\mathbf{D_Q}$	20	4 or 5	3, 4, 6–9	Nispen et al. (1980), Waetjen (1987), Waetjen and Hansen (1988), Hansen and Waetjen (1989a, 1990, 1991, b, c), TenBrink et al. (1992, 1993, 1994, 1996), Jacobsen et al. (1996a, b, 1999), Mickelson et al. (1996), Chen et al. (2001, 2002a), Hazeldine et al. (2005)
$\mathbf{E1_Q}$	1	3–5	1, 5	Mamedov et al. (2011)
$\mathbf{A1_I}$	2	3	–	Malamas et al. (2010, 2011b)
$\mathbf{A2_I}$	7	2	3, 6–9	Lee and Brown (1983, 1984), Pierre et al. (2012), Chen et al. (2004a, b), Borchardt et al. (2011b), Kim et al. (2011), DeMoliner and Hulme (2012a, b), Van Leusen and Van Leusen (2012)
$\mathbf{A4_I}$	4	2 or 3	6–9	Adegoke and Alo (1983), Basanagoudar et al. (1991), Silvestri et al. (2000), Barrish and Spergel (2001), DeMoliner and Hulme (2012a)
$\mathbf{B1_I}$	11	3–5	1–4, 6–9	King and Clark-Lewis (1951), Davey et al. (1991), Davey (1999), Shaw (1992, 1993a, b, c, 1995), Colotta et al. (1995), Ohmori et al. (1997), Kundu et al. (2005), Okada et al. (2009), Kaizawa et al. (2011), Verma et al. (2013)

Note Here and in Table 4.5, a dash means that substituents cannot be varied

quinoxaline **177** from 1-morpholino-2-dicyanomethylideneiminocyclohexene **176** and ethyl glycinate hydrochloride (Legroux et al. 1987), offers great potential for creating imidazoquinoxaline systems from compounds containing neither the quinoxaline nor the imidazole ring.

Table 4.5 Comparison of different approaches to the synthesis of imidazo[1,2-*a*]quinoxalines (see Figs. 4.5 and 4.6)

Variant	Number of studies	Number of stages	Substituent variation positions	References
A1$_Q$	13	4–5	1, 2, 4, 6–9	Heine and Brooker (1962), Hirotaka et al. (1970), McQuaid et al. (1992), Albaugh and Hutchison (1993, 1995), Ohmori et al. (1997), Caamano et al. (2000), Parra et al. (2001), Deleuze-Masquéfa et al. (2004, 2010), Liu et al. (2004), Borchardt et al. (2010), Kim et al. (2011)
A3$_Q$	3	3	2 or 4	Ramm and Barnes (1980), Ager et al. (1988), Parra et al. (2001)
B3$_Q$	1	3	2, 6–9	Hariharakrishnan et al. (2008)
C1$_Q$	3	4	1, 2	Catarzi et al. (1994), Albaugh and Hutchison (1995), Teranishi (2007)
D$_Q$	1	1	–	Poursattar et al. (2012)
E1$_Q$	2	2	1, 2, 4, 6–9	Krasavin and Parchinsky (2008), Krasavin et al. (2009)
A1$_I$	11	4	4	Warner and Luber (1979a, b, c, 1980a, b, c, d, e), Lamberth (1999), Chen et al. (2002b)
A2$_I$	4	2	6–9	Simonov and Uryukina (1971), Simonov et al. (1972), Uryukina et al. (1972), Li et al. (2013), Scott and Söberberg (2002)
A4$_I$	2	2	6–9	Deleuze-Masquéfa et al. (2009c, 2010), Huang et al. (2013b)
B1$_I$	9	3	1, 2, 4, 6–9	Davey et al. (1991), Colotta et al. (1995), Jeppesen (1995), Treiber et al. (1996, 1997), Ohmori et al. (1997), Campiani et al. (1999), Chen et al. (2002a, 2011)
D1$_I$	4	1	1, 2, 4, 6–9	Strauss et al. (1978), Parthasarathy et al. (1983), Ellames and Jaxa-Chamiec (1987), Reeves et al. (2010), Huang et al. (2013a)

We hope that information presented in this chapter will be helpful for researchers dealing with the chemistry of fused heterocycles not only to reduce the time for the search for and development of a synthetic approach to target compounds from readily available derivatives but also to invent radically new methods of synthesis of fused systems with a known combination of heterocycles. In our opinion, this work can stimulate synthetic organic chemists to design a wide range of new pharmaceutically promising compounds.

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Chapter 5
Synthesis of Quinoxaline Macrocycles

5.1 Introduction

Macrocyclic compounds are widespread in nature. These are porphyrins (chlorophyll, heme as a part of hemoglobin, Vitamin B12), cyclic peptides (antibiotics gramicidin C, capreomycin, valinomycin, vancomycin, amato, and fallotokcins of death cup amanita (Amanita phalloides) and some toadstools), macrocyclic alkaloids (including tubocurarin–the main component of the Indian poison curare), cyclic ketones and lactones (musk highlight animals), and many others. They play a crucial role in the chemical processes occurring in the environment, in the functioning of living systems. For example, the key role in the implementation of photosynthesis by molecules of chlorophyll involves the formation of supramolecular assemblies, the ordered structure of the photo center that contributes to the multistage charge transfer. Supramolecular interactions in the processes of the oxygen transport by hemoglobin causes conformational changes that increase the binding constant of oxygen, such as myoglobin which is not typical. The B12 vitamin (its active forms are cyanocobalamine, adenosylcobalamine or cobalamine) possesses a pronounced lipotropic effect, prevents the fatty infiltration of a liver, increases the consumption of oxygen by cells in acute and chronic hypoxia, participates in the processes of transmethylation, hydrogen transfer, activates methionine synthesis, possesses an anabolic effect, increases the immunity, takes part in the synthesis of the purine and pyrimidine bases which are a part of nucleinic acids, necessary for the erythropoiesis process, and actively influences the accumulation of compounds containing sulfhydryl groups in erythrocytes.

In their daily practice, people have always sought to copy and use the processes occurring in nature, which was associated with great and sometimes insurmountable difficulties. Thanks to the achievements of supramolecular chemistry and nanotechnology, there have recently appeared new opportunities in this direction. Currently, a wide range of analogs of the natural macrocyclic compounds which have found application in various areas of science and technology has been

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synthesized. Among them numerous porphyrines and their derivatives, i.e., phthalocyanines, porphyrazines, and other compounds of the tetrapyrrole classes (Sessler et al. 2006), analogs of macrocyclic polyamide-antibiotics (Mallinson and Collins 2012), known as crown ethers, cryptophanes, spherands, hemispherands, calixarenes, other cyclophanes with the various heterocyclic structural blocks (Steed and Atwood 2000; Sessler et al. 2006). Compounds, which combine two types of macrocyclic structures, such as crown-substituted phthalocyanine and porphyrin, opening new opportunities for the design of supramolecular systems and architectural compositions, have also been synthesized (Suksai and Tuntulani 2003).

Much less attention has been paid to the macrocycles, which are not a part of classical macrocyclic systems, such as crown ethers, cryptophanes, spherands, hemispherands, calixarenes, porphyrins, etc., consisting of separate structural fragments of these macrocycles. In this regard, quinoxalines, as starting materials for the creation of complex heterocyclic compounds, including macrocyclic structures, are of great interest for synthetic chemists and biochemists. The above structures are important components with more than 50 drugs and their analogs (Negwer and Scharnow 2001). The development of the methods for the synthesis and study of the properties of the macrocyclic structures with quinoxaline moieties becomes one of the trends of the development of supramolecular chemistry and pharmacology. Methods for creating the quinoxaline macrocycles can be divided into four groups: (1) the introduction of the quinoxaline system into the structure of the already existing macrocycle, (2) the construction of macrocyclic systems based on different derivatives of quinoxalines, (3) the construction of macrocyclic systems based on the podands having quinoxaline fragments at the terminal positions of oligo(ethylene glycol) or other spacers, and (4) other methods.

5.2 The Introduction of the Quinoxaline System into Macrocycles

The methods used for the introduction of the quinoxaline system into the structure of macrocycles are based on the Hinsberg–Körner, Beirut (the latter is also known as the Haddadin–Issodorides reaction), Diels–Alder and Williamson reactions. The first group includes the reaction of macrocycles **1–3** and **6**, containing 1,2-diaminobenzene (1,2-DAB) and benzofuroxan (i.e., benzofurazan *N*-oxide) moieties, which are the suppliers of a two-carbon fragment. Thus, the DAB moiety is attached to the macrocyclic system via the nitrogen or carbon atoms. The second method involves the reaction of macrocycles **4**, **5**, containing a 1,2-dicarbonyl fragment with the 1,2-DAB derivatives. The third one is a reaction of porphyrins **7** with the pyrazine *o*-quinodimethane. The fourth method is based on the reaction of calixrezorcinarens **8** with the 2,3-dihloroquinoxalines.

The formulas of macrocycles–predecessors of quinoxaline macrocycles–are presented below (Fig. 5.1).

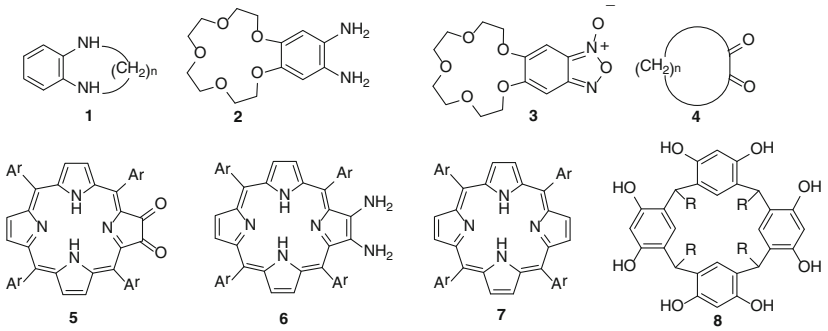
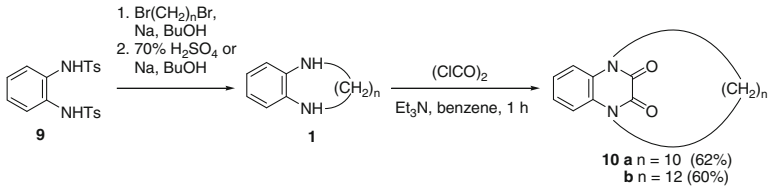


Fig. 5.1 Precursors of the quinoxaline macrocycles



Scheme 5.1 Synthesis and transformation of *N,N'*-polymethylene-1,2-DABs to corresponding quinoxalin-2,3(1*H*,4*H*)-diones

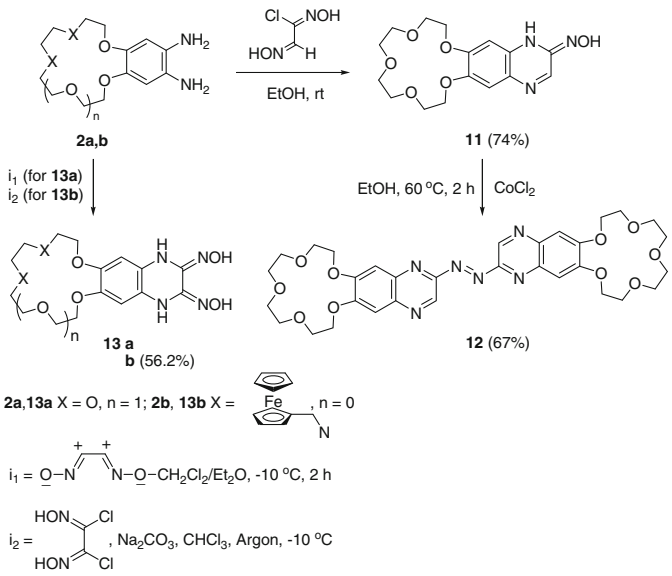
5.2.1 N,N′-*Polymethylene-1,2-Diaminobenzenes*

The first representatives of quinoxaline macrocycles in the formation of a macrocyclic skeleton, the quinoxaline system, delivers a four-atomic fragment N–C–C–N are *N,N′*-deca(dodeca) methylenequinoxalin-2,3(1*H*,4*H*)-diones **10** (Scheme 5.1). They were obtained in 1975, by Hayward and Meth-Cohn (1975), by the interaction of oxalyl chloride with the *N,N′*-polymethylene-1,2-DABs **1**.

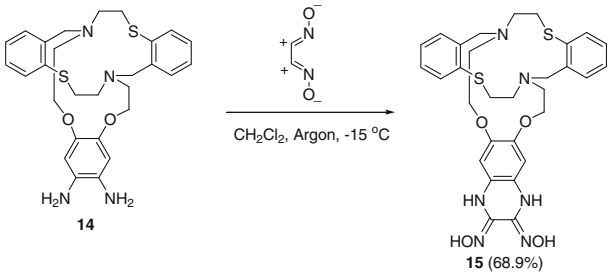
The earlier members of this series (n = 2–6) had been prepared by Stetter (1953) when *N,N′*-ditosyl-1,2-DAB is affected by α,ω-dibromoalkane, followed by the hydrolysis of the ditosyl derivative **9**.

5.2.2 *Crown Ethers with Diaminobenzene and Benzofuroxane Moieties*

The condensation of 2,3-diaminobenzo-15-crown-5 **2a** with *s-trans*-chloroethanedial dioxime proceeds with the formation of the (15-crown-5)eno[*g*]quinoxaline-2(1*H*)-one oxime **11**, which when heated in absolute ethanol at 60 °C in the presence of $CoCl_2$ for 4 h results in 2,2′-azobis[(15-crown-5-eno[*g*]quinoxaline)] **12**



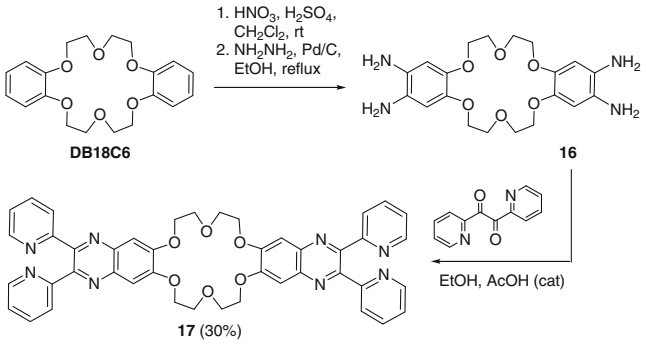
Scheme 5.2 Synthesis of crown ethers with diaminobenzene and benzofuroxane moieties



Scheme 5.3 Synthesis of dioxadithiadiazamacrobicycle with quinoxaline (*E*,*E*)-dioxime moiety

(Scheme 5.2) (Gull et al. 1986a). The use of cyanogen-di-*N*-oxide and (*E*,*E*)-dichloroglyoxime instead of the *s-trans*-chloroethanedial dioxime in the reaction with 2,3-diaminobenzo-15-crown-5 **2a** and 12,13-diamino-4,7-bis(ferrocenylmethyl)-2,3,4,5,6,7,8,9-octahydrobenzo[*k*]-4,7-di-aza-1,10-dithiacyclododecine **2b** makes it possible to synthesize the macrocyclic dioximes **13a**, **b** (Gull et al. 1986b; Ertas et al. 2007).

Cyanogen-di-*N*-oxide appeared to be a convenient reagent for the synthesis of quinoxaline substituted (*E*,*E*)-dioxime with a dioxadithiadiazamacrobicycle **14** when interacting with the 2,3-diaminobenzene attached to the mixed-donor-macrobicycle **15** (Scheme 5.3) (Kantekin et al. 2002).



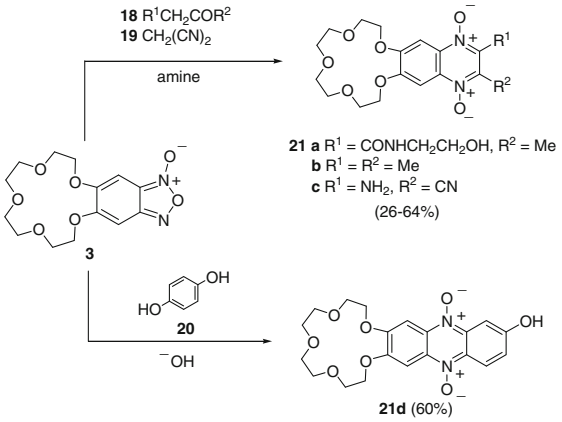
Scheme 5.4 Synthesis of 18-crown-6 with two dipyridylquinoxaline moieties

In 2012, Xian-He Bu and co-workers reported a new chemosensor, 2,3,15,16-tetrakis(pyridin2-yl)-7,8,10,11,20,21,23,24-octahydro[1,4,7,10,13,16]-hexaoxacyclooctadecino[2,3-*g*:11,12-*g*′]diquinoxaline **17**, containing 2,3-bis (pyridin-2-yl)quinoxaline and crown ether moieties, which had been designed and found to be a ratiometric and selective fluorescent detector of Zn^{2+} over a wide range of tested metal ions (Scheme 5.4) (Li et al. 2012). The addition of Zn^{2+} to the solution of **17** in acetonitrile induced the formation of a 1:2 ligand-metal complex, **17**-Zn^{2+}, which due to the mechanism of internal charge transfer has exhibited a remarkable enhanced fluorescent emission centered at 460 nm, with the disappearance of the fluorescent emission of **17** centered at 396 nm. In contrast, the presence of K^+ results in the fluorescence quenching of **17** and **17**-Zn^{2+} through the photoinduced electron-transfer mechanism. These results demonstrate that **17** can perform as not only an INHIBIT logic gate but also an "off-on-off" molecular switch triggered by Zn^{2+} and K^+ (Li et al. 2012). Fluorophore **17** has been synthesized from DB-18-crown-6 according to the following sequence (Duggan et al. 2001; Li et al. 2012).

An extension of the Beirut reaction for the preparation of the first members of the quinoxaline 1,4-dioxideannulated crown ether series has been described (Förster et al. 1985; Niclas et al. 1985). Benzofuroxan-15-crown-5 **3** in MeOH reacts with various ketones **18** in the presence of $HOCH_2CH_2NH_2$ or NH_3. It also reacts in DMF with malononitrile **19** in the presence of Et_3N and leads to the annulated crown ethers **21a–c** with the phenazine di-*N*-oxide moieties. In the 50 % aqueous NaOH solution with the hydroxyquinone **20,** the annulated crown ether **21d** with the phenazine di-*N*-oxide moiety is produced as well (Niclas et al. 1985) (Scheme 5.5).

5.2.3 Macrocyclic Diketones

Cyclic diketones can be the predecessors of quinoxaline macrocycles, obtained in one stage with the oxidation of cyclic alkenes with potassium permanganate



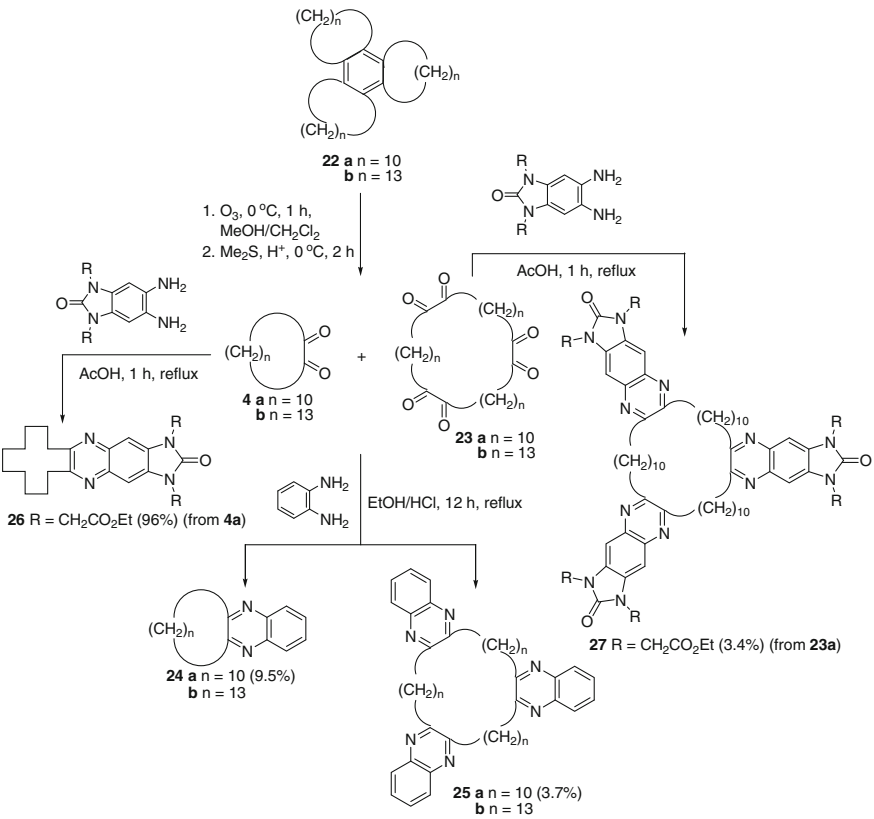
Scheme 5.5 Synthesis of the quinoxaline- and phenazine-di-*N*-oxideannulated crown ether series

(Sharpless et al. 1971) or in two stages by the cyclotrimerization of cyclic alkynes and subsequent ozonolysis of compounds **22** (Scheme 5.6) (Mandeville and Whitesides 1986). Along with the formation of diketone **4,** the latter reaction leads to the unstable hexaketone **23**. The reaction of the mixture of compounds **4** and **23** with the 1,2-DAB leads to macrocycles **24** and **25** with one or three quinoxaline fragments, respectively, with ∼10 and ∼4 % yields, calculated in two stages. The synthesis of the macrocycle **26** from the analytically pure diketone **4a** was in quantitative yield.

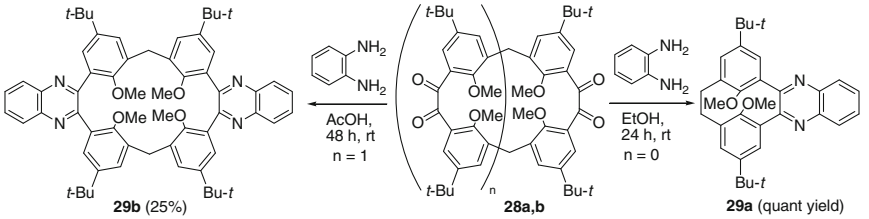
The interaction of [2.2]metacyclophane-1,2-dione **28a** ($n = 0$) with the 1,2-DAB in ethanol for 24 h at room temperature resulted in the desired [2.2]metacyclophane **29a** an almost quantitative yield having a quinoxaline skeleton (Yamato et al. 2000), whereas the tetracarbonyl derivative **28b** ($n = 1$) easily available by the Albright–Goldman oxidation of 5,12,20-tetra-*tert*-butyl-1,2,16,17-tetrahydroxyl-8,15,23,30-tetramethoxyl-2.1.2.1]metacyclophane (Sawada et al. 2006) yielded [2.1.2.1]metacyclophane **29b** with two quinoxaline skeletons in 25 % yield only when condensed with the 1,2-DAB (Nishiyama et al. 2007) (Scheme 5.7).

5.2.4 Porphyrins

The introduction of the quinoxaline system in the porphyrins is achieved by (a) the condensation of the dioxoporphyrins with 1,2-DABs, (b) the condensation of the diaminoporphyrins with 1,2-diketones, and (c) the reaction of porphyrins with *ortho*-quinodimetane. The first two approaches represent the Hinsberg–Kĕrner reaction and the third approach deals with the Diels–Alder reaction.



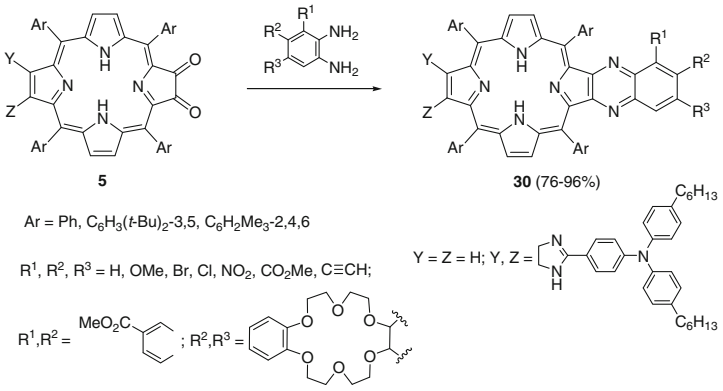
Scheme 5.6 Syntheses of macrocyclic trisquinoxalines



Scheme 5.7 Synthesis of quinoxalinophanes possessing one and two quinoxaline rings system at the bridge moieties

5.2.4.1 *Meso*-tetraaryldioxoporphyrins

The interaction of porphyrin-α-diones **5** with the 1,2-DABs leads to the quinoxalinoporphyrins **30** (Duggan et al. 2001; Spence et al. 2004; Kadish et al. 2007; Crossley et al. 2008; Eu et al. 2008; Kira et al. 2010; Hayashi et al. 2013)



Scheme 5.8 Synthesis of quinoxalinoporphyrins possessing one quinoxaline ring system

(Scheme 5.8). Most of these reactions are usually carried out in a solution of methylene chloride at room temperature from 10 min to 1 h to form quinoxalinoporphyrins in nearly quantitative yields. If there are electron acceptor groups at the structure of the 1,2-DABs, the reaction mixture is boiled for some hours or is mixed for several days at the room temperature.

The push–pull quinoxalino[2,3-*b*]porphyrin acid **30** (Ar = 2,4,6-trimethylphenyl, $R^1 = R^2 = H$, $R^3 = CO_2H$; Y, Z = 2-(4-dihexylphenylaminophenyl)imidazo-4,5) (ZnPQI) with an electron-donating triarylamino group at the β,β′-edge through a fused imidazole group and an electron-withdrawing carboxyquinoxalino anchoring group at the opposite β,β′-edge (ZnPQI) evaluated the effects of the push–pull structure of ZnPQI on optical, electrochemical, and photovoltaic properties. ZnPQI showed the red-shifted Soret and Q bands relative to the reference porphyrin with only an electron-withdrawing group (ZnPQ), thus demonstrating the improved light-harvesting property of ZnPQI. The optical HOMO–LUMO gap was consistent with that estimated by the DFT calculations. The ZnPQI-sensitized solar cell exhibited a relatively high power conversion efficiency (η) of 6.8 %, which under optimized conditions is larger than that of the ZnPQ-sensitized solar cell ($\eta = 6.3$ %) (Fig. 5.2). The short-circuit current and fill factor of the ZnPQI-sensitized solar cell are larger than those of the ZnPQ-sensitized solar cell, whereas the open circuit potential of the ZnPQI-sensitized cell is smaller than that of the ZnPQ-sensitized cell, which leads to the overall improved cell performance of ZnPQI (Hayashi et al. 2013). Such fundamental information provides a new tool for the rational molecular design of highly efficient dye-sensitized solar cells based on push–pull porphyrins (Eu et al. 2008; Hayashi et al. 2013).

For the synthesis of bis-quinoxalineporphyrins porphyrins with either the two α-dioxofragments (Wenbo et al. 2008) or the quinoxalineporphyrins with one α-dionefragment (Crossley et al. 1991; Eu et al. 2008; Imahori et al. 2011) are used. As a result of the condensation of compounds **31** and **32** with the 1,2-DABs the linear bis-quinoxalineporphyrins **33** have been synthesized (Scheme 5.9). The

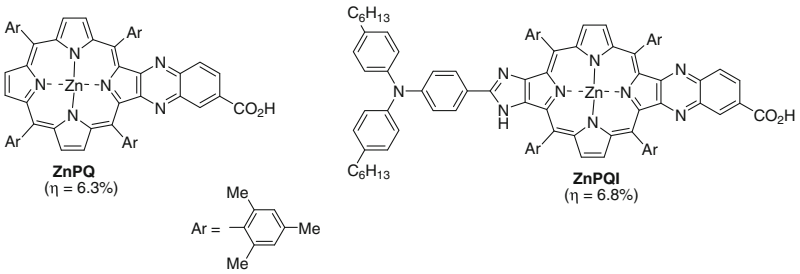
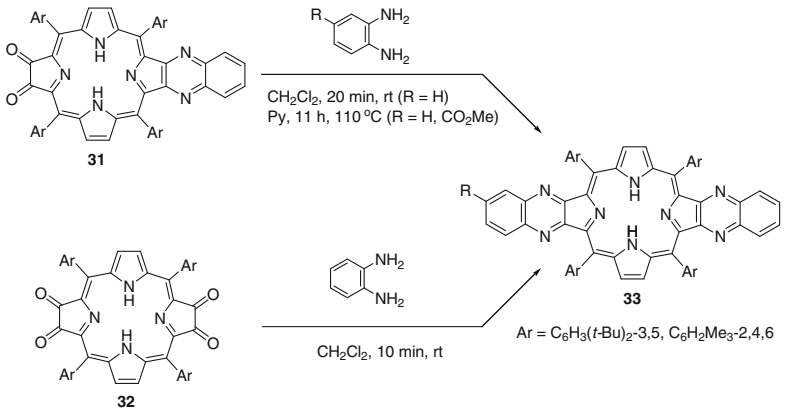


Fig. 5.2 Quinoxalinoporphyrins possessing one quinoxaline ring system and both quinoxaline and imidazole ring systems at the bridge moieties



Scheme 5.9 Two alternative approaches for the synthesis of bis-quinoxalineporphyrins

angular bis-quinoxalineporphyrins **34** were synthesized in a similar way (Fig. 5.3) (Wenbo et al. 2008).

The synthesis of the tris-quinoxalineporphyrins **35** is possibly the result of the condensation of 1,2-DABs with the (a) angular and (b) linear quinoxalineporphyrins, with a α-dionefragment, and (c) quinoxalineporphyrins with two α-dionefragments. All the three strategies were successfully realized (Khoury and Crossley 2009) (Fig. 5.3). The condensation of 1,2-DABs with the tris-quinoxalineporphyrin-α-diones results in the tetra-quinoxalineporphyrins **36** (Fig. 5.3) (Khoury and Crossley 2007).

The α-dionefragment in the porphyrin system is generated by a four-stage process involving the synthesis of the zinc or copper complex, its interaction with nitrogen dioxide in petroleum ether, demetallation under the influence of HCl, the reduction of the nitro group to the amino group with the tin chloride (II), and its oxidation with oxygen when exposed to light (Khoury and Crossley 2007, 2009) (Scheme 5.10). Introduction of the nitro group can also be carried out by reaction of a copper complex of porphyrin derivative with the $Cu(NO_3)_2$ in a mixture of acetic

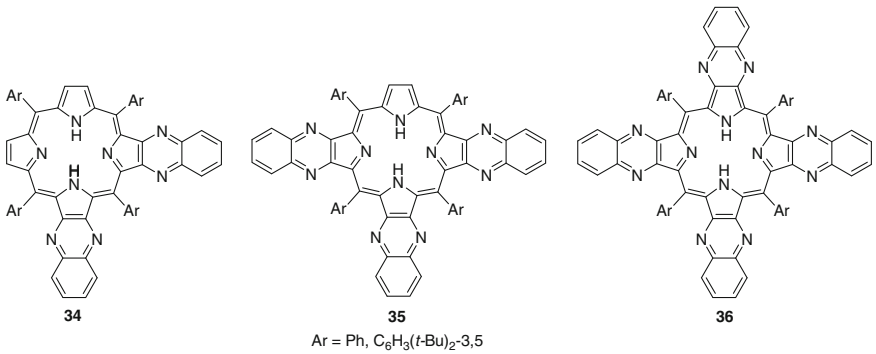
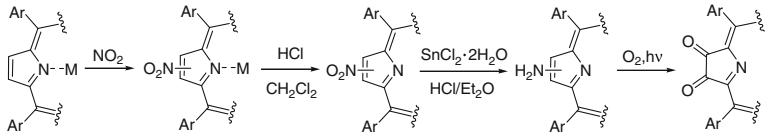


Fig. 5.3 Quinoxalineporphyrins with two, three and four quinoxaline moieties



Scheme 5.10 Succession of the reactions for introduction of α-dionefragment in pyrrole ring

anhydride, acetic acid, and chloroform, and as a reducer of nitro-group to use $NaBH_4$/Pd(C). The subsequent final stage of oxidation is carried out using Dess–Martin–Periodinane oxidation (DMP) (Eu et al. 2008). An alternative strategy is the introduction of an acetate moiety (Crossley et al. 1991; Hayashi et al. 2013). The formation dioxo-moiety occurs in three steps: by the reaction of porphyrin derivative with silver acetate, in the presence of iodine, subsequent hydrolysis under the influence of K_2CO_3, and further DMP (Hayashi et al. 2013). The overall yield of the process is 20 % (Crossley and King 1984; Promarak and Burn 2001; Khoury and Crossley 2007, 2009).

When compounds with four amino groups (1,2,4,5-tetrahydrochloridete traminobenzene (Crossley and Burn 1987; Crossley et al. 1995a, b; Beavington and Burn 2000a, b; Sendt et al. 2002), 2,3,5,6-tetramino1,4-benzoquinone (Sendt et al. 2002; Crossley and Johnston 2002), tetrahydrochloride 3,3′-diaminobenzidine (Crossley et al. 1996b, 2003), tetraminodibenzo-18-crown-6, tetraminodibenzo-24-crown-8 and tetraminodibenzo-30-crown-10 (Duggan et al. 2001) are used instead of 1,2-DAB macrocycles are obtained with two quinoxalineporphyrin fragments **37**–**40**. The interaction of the tetrahidrochloride 1,2,4,5-tetraminobenzene with the dioxoporphyrine **5** and the 1,10-phenanthroline-5,10-dione or other diones which followed led to compounds of the type of **41** (Crossley et al. 1995a; Crossley and Johnston 2002; Gaynor et al. 2006) (Fig. 5.4).

The possibility of the introduction of one or two α-dione groups into the composition of porphyrines opens the vistas to various laterally extended oligo-porphyrin systems **42**–**44** (Crossley et al. 1995b, 2005; Gaynor et al. 2006) (Fig. 5.5).

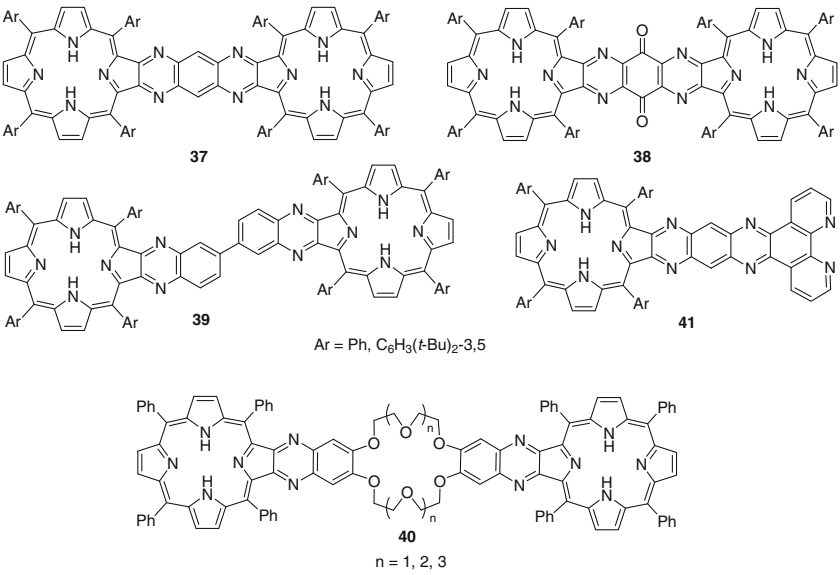


Fig. 5.4 Bi- and bis-quinoxalinyl bridged bis-porphyrins

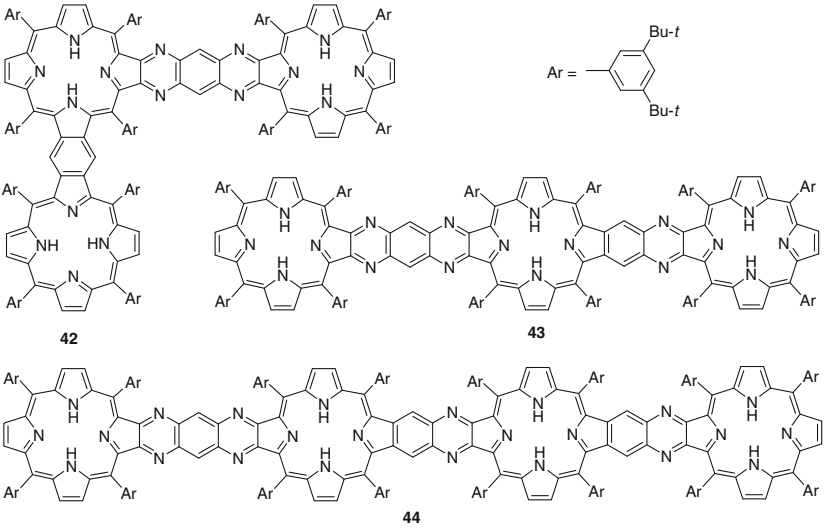


Fig. 5.5 Bi- and bis-quinoxalinyl bridged bis-, tris- and tetra-porphyrins

The condensation of chlorin[1] **45** with the 1,2-DAB and 2,3-diaminonaphtalene (2,3-DAN) in the presence of catalytic amounts of the trifluoroacetic acid (TFA) leads to a mixture of three compounds. The main product of the reaction, i.e., quinoxaline [2,3-*n*]pheophorbide **46** is formed in 52–55 % yields (Scheme 5.11). The two other reaction products were the benzimidazole derivatives of chlorine, i.e, isomers **47** and **48** (Kozyrev et al. 2000). The macrocycle **46** appears to be stable to the heating in pyridine in the presence of TFA. While the interaction of chlorine **45** with the 1,2-DAB in the presence of a large excess of the TFA increases the yield of compound **47** up to 64 % and makes it the major reaction product. Under these conditions, the yield of its benzimidazole analog **48** increases but negligibly. The replacement 1,2-DAB and 2,3-DAN on 1.8-diaminonaphtalene or 9.10-diaminophenantrene leads to a more selective course of the reaction and the formation of the compound **47** as a sole product of the condensation (Kozyrev et al. 2000).

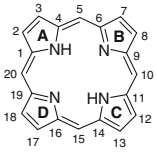
The condensation of chlorin[1] **45** with the tetrahydrochloride 1,2,4,5-tetraminobenzene at room temperature for 5 days in the solution of methylene chloride in the presence of a catalytic amount of TFA led to the compounds **49** and **50** in 23 and 8 % yields, respectively (Kozyrev et al. 2000) (Fig. 5.6).

5.2.4.2 *Meso*-tetraaryldiaminoporphyrins

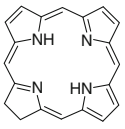
The reaction of *o*-diamines **6** with *o*-benzoquinone or cyclohexane-1,2-dione is used for designing of quinoxaline system in porphyrins (Scheme 5.12) (Crossley et al. 1996a). In this case, in contrast to the classical reaction of Hinsberg–Körner there occurs the quinoxalineannulation of the system to which the diamine moiety belongs.

This approach for the synthesis of macrocycles with quinoxaline moieties involves the development of methods for the introduction of amino groups to the adjacent carbon atoms of the planned unit of the macrocycle system. Two methods (Crossley et al. 1996a) have been developed for the synthesis of diaminoporphyrin **6**. The first involves the reduction of the nitro group to the amino group of the compound **53** with sodium borohydride in the presence of the Pd/C and subsequent regioselective nitration (Scheme 5.13). The second one is the nucleophilic substitution of hydrogen by NaNHCHO and subsequent hydrolysis. Both methods lead to

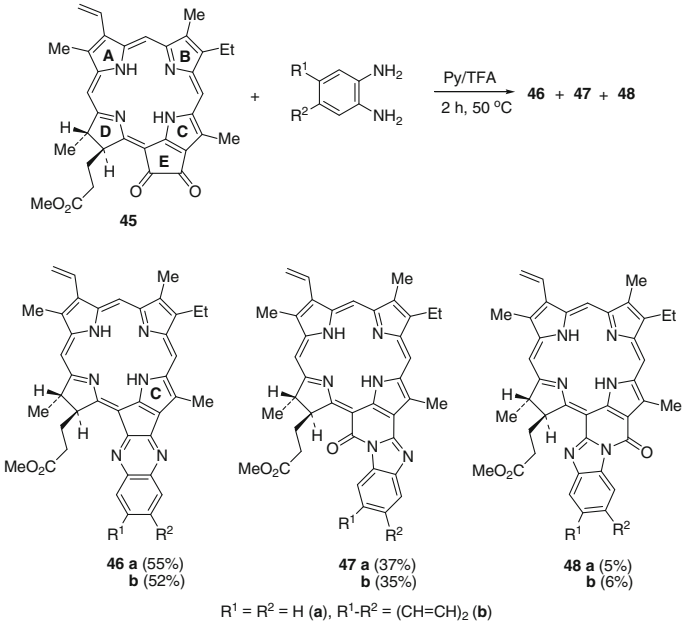
[1]**Chlorin** is a large heterocyclic aromatic ring with three pyrroles and one pyrroline coupled through four = CH-linkages at the core. Unlike porphin the central aromatic ring structure of porphyrins, a chlorin is therefore largely aromatic but not aromatic through the entire circumference of the ring. In porphyrin not only the number of peripheral π-electrons is 18, but the total number of electrons is 26, which also corresponds to the Hückel rule.



porphyrin



chlorin



Scheme 5.11 The reaction of chlorin with the 1,2-DAB and 2,3-diaminonaphtalene

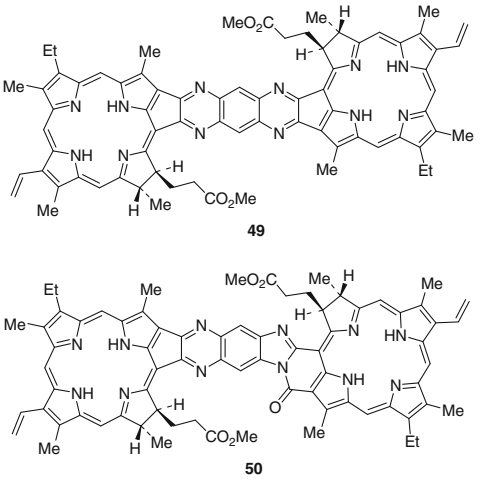
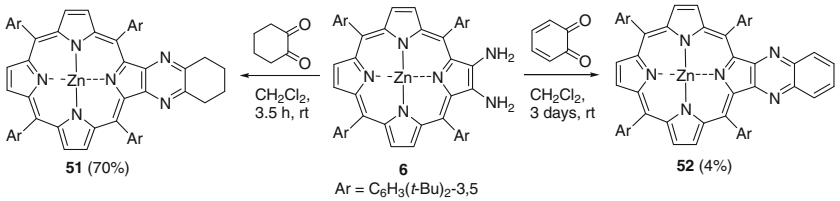
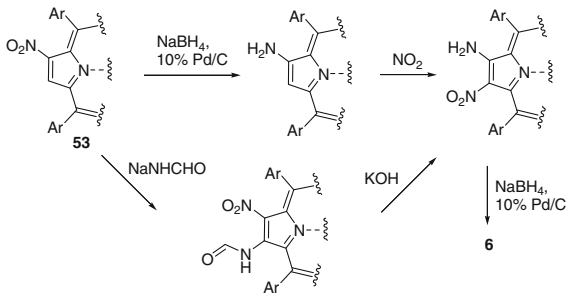


Fig. 5.6 Products of the reaction of chlorin with the tetrahydrochloride 1,2,4,5-tetraminobenzene

the diaminoporphyrin **6** in satisfactory yields. However it should be noted that obtaining quinoxalineporphyrins from diaminoporphyrin **6** did not find any broad application unlike the condensation of α-diketoporphyrin **5** with the 1,2-DABs (see Sect. 5.2.4.1).



Scheme 5.12 Condensation of *o*-diamine porphyrins with *o*-benzoquinone or cyclohexane-1,2-dione

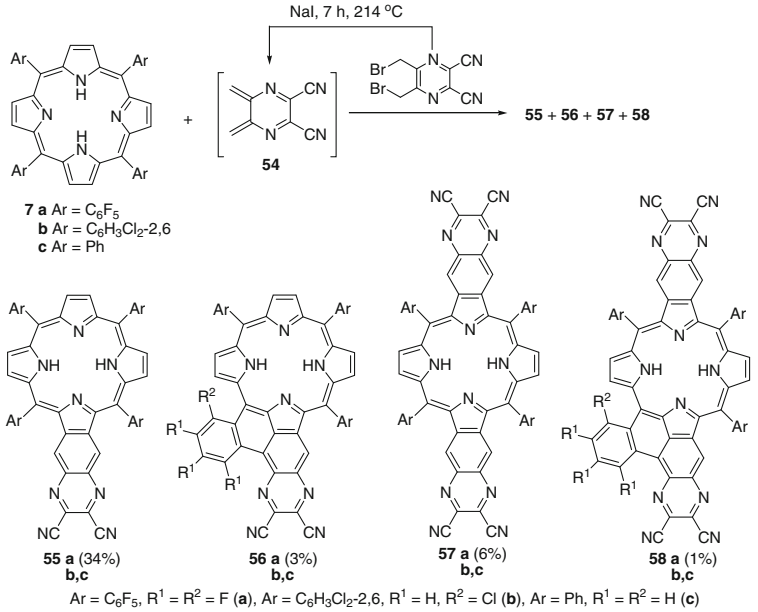


Scheme 5.13 Succession of the reactions for introduction of α-diamine groups in pyrrole ring

5.2.4.3 *Meso*-tetraarylporphyrins

The Diels–Alder reaction of *meso*-tetraarylporphyrins with the pyrazine *o*-quinodimethane mainly affords the oxidized compounds **55a–c** instead of the expected chlorin adducts (Scheme 5.14). The bis-addition is site specific, occurring in opposite pyrrolic rings and leads to compounds **57** and **58**. The novel polycyclic products **56a–c**, **58a,** and **58b** result from the coupling reactions between the β-fused quinoxaline ring and one adjacent *meso*-aryl group. It should be pointed out that, in contrast to compounds **55a** and **57a**, there also occurs the combination between one of the *orto*-atoms of the carbon of the *meso*-aryl group and one of the carbon atoms of the benzene ring quinoxaline system in the formation of compounds **56a** and **58a**.

Quite similar results were obtained with porphyrin **7b**. In this case, the formation of compounds **56b** and **58b** resulted from the elimination of HCl from **55b** and **57b**, respectively. Since porphyrin **7c** as a dienophile is much less reactive than **7a** and **7b**, and since there are no halogen atoms at the *meso*-phenyl groups, only the monoaddition product **55c** was expected. However, surprisingly, together with the **55c** (3 % yield), a reasonable amount of **56c** (16 % yield) appeared as well. Since the formation of **56c** could not result from the elimination of HX in this case, it was possibly formed by an oxidative coupling reaction. The formation of **56c** was attempted by refluxing **55c** in chloroform in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone was unsuccessful. Also refluxing **55a**, **b** and **c** in 1,2,4-trichlorobenzene did not afford the corresponding derivatives **56**.



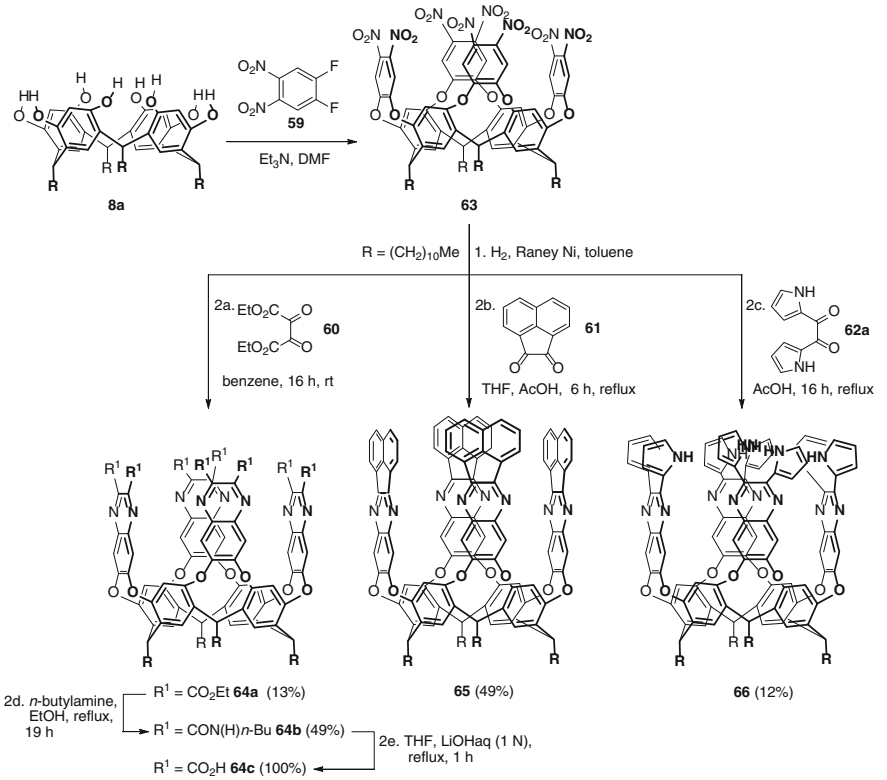
Scheme 5.14 The Diels–Alder reaction of *meso*-tetraarylporphyrins with the pyrazine *o*-quinodimethane

These experiments seem to indicate that the coupling process must occur before the aromatization of the Diels–Alder adduct (Zhao et al. 2005). Quinoxalineporphyrin **55d** (Ar = $C_6H_2Me_3$) was obtained (Kira et al. 2010) from the corresponding porphyrin **7** with the use of the methodology developed in (Zhao et al. 2005).

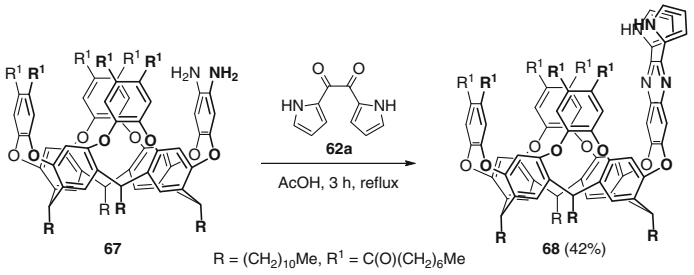
These π-extended porphyrin derivatives show the absorption bands at wavelengths higher than 700 nm. This is important for their potential use as photosensitizers in the photodynamic therapy (PDT) of tumors.

5.2.5 Resorcin[4]arene Cavitands

The deeper cavitands are usually prepared by bridging the resorcinarene hydroxyl groups of **8a** with a preformed heterocycle, e.g., condensation with a 6,7-disubstituted-2,3-difluoroquinoxaline (Rudkevich et al. 1998). The alternative involves the use of a simpler building block in the bridging reaction and then extension of the rim through heterocyclic synthesis (Tucci et al. 1999). Specifically, the octanitro cavitand **63** (Rudkevich et al. 1997, 1998) was obtained by reaction of **8a** with 1,2-difluoro-4,5-dinitrobenzene **59** (Kazimierczuk et al. 1981) in DMF at 70 °C in the presence of Et_3N. The NO_2 groups were hydrogenated with Ra/Ni in toluene, and the corresponding phenylenediamine units were condensed with



Scheme 5.15 Synthesis of the deeper cavitands



Scheme 5.16 Synthesis of the hexaamide cavitand with the dipyrrolylquinoxaline moiety

1,2-diketones. The resulting fused pyrazines provide the deepened cavities. Diethyl 2,3-dioxosuccinate **60**, acenaphthenequinone **61** and 2,3-(dipyrrol-2-yl)ethanedione **62a** (Oddo 1911; Behr et al. 1973) formed cavitands **64**, **65** (Rudkevich et al. 1998; Tucci et al. 1999) and **66** (Lücking et al. 2000), respectively, as yellow solids in 13, 49, and 12 % (Scheme 5.15). Lehn and others utilized a similar heterocyclization strategy to construct helicates and extended surfaces (Wärnmark et al. 1996; Warrener et al. 1998).

Hexaamide cavitand **68** was prepared similarly (42 % yield) from **62a** and diamine cavitand **67** (Scheme 5.16). It has been shown that cavitands **66** and **68** can be used as visual detectors of fluoride and acetate anions (as tetrabutylammonium salts) in aprotic solvents such as acetone and CH_2Cl_2 (Lücking et al. 2000).

5.3 Quinoxaline Derivatives in the Synthesis of Macrocycles

Quinoxalin-2,3(1*H*,4*H*)-dione **69**, 2,3-dichloroquinoxalines **70**, quinoxalin-2,3(1*H*,4*H*)-dithione **71**, 2,3-dibromomettylquinoxalines **72**, 4-[3-(4-hydroxyphenyl)-2-quinoxalinyl]phenol **73a**, 4-[3-(4-mercaptophenyl)-2-quinoxalinyl]thiophenol **73b**, 2,3-dipyrrolylquinoxalines **74** and **75b**, 2,3 dicyanoquinoxaline **76a** and its benzo[*f*]–**76b** and the dibenzo[*f*,*h*]–**76c** annulated derivatives as well as 6,7-dicyanoquinoxalines **77** were used among the numerous derivatives of quinoxaline as key compounds for designing of the quinoxaline macrocycles (Fig. 5.7).

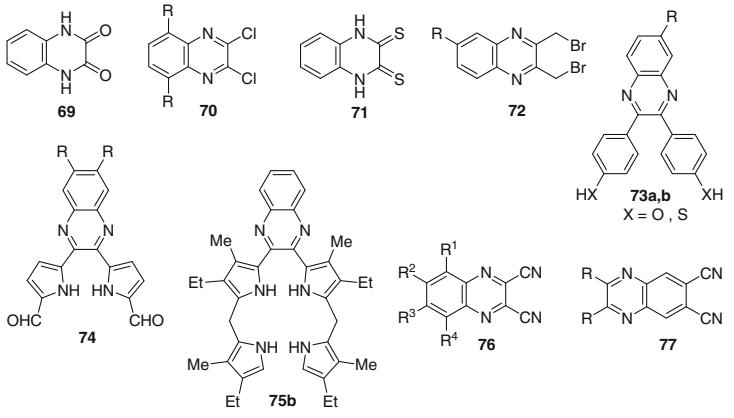
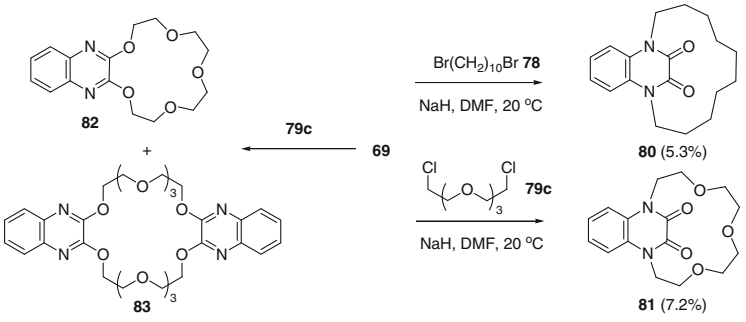


Fig. 5.7 Quinoxaline derivatives–precursors of the quinoxaline macrocycles

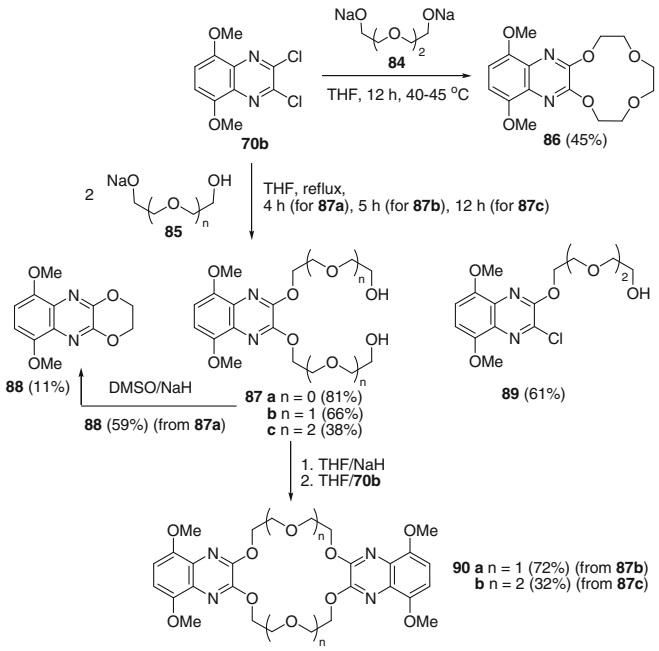
5.3.1 *Quinoxalin-2,3(1H,4H)-dione, 2,3-Dichloroquinoxaline and Quinoxalin-2,3(1H,4H)-dithione*

The interaction of quinoxalin-2,3(1*H*,4*H*)-dione **69** with 1,10-dibromodecane **78** and 1,11-dichloro-3,6,8-trioxaundecane **79c** leads to the products of di-*N*-alkylation–1,4-quinoxalinacyclophanes **80** and **81** (Scheme 5.17) (Htay and Meth-Cohn 1976a, b). A more recent study of the reaction of compound **69** with 1,11-dichloro-3,6,8-trioxaundecane **79c** under phase-transfer catalysis conditions showed that in this case the reaction products are macrocycles of another structure with one **82** or two **83** quinoxaline structural blocks, formed as a result of di-*O*-alkylation and attached to each other by polyether units (Scheme 5.17) (Ferfra et al. 2005).

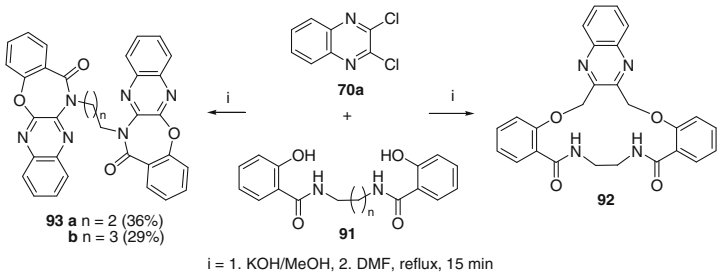
When 2,3-dichloroquinoxaline **70** and 1,*n*-glycols are used instead of quinoxalin-2,3(1*H*,4*H*)-dione **69** and 1,*n*-dihaloalkanes as starting compounds for the synthesis of quinoxaline macrocycles regioselectively is possible with the formation of only 2,3-quinoxalina-crown ethers **86** or their open-chain analogs with the quinoxaline moiety **87a–c** (Scheme 5.18). This makes it possible in reactions with the second molecule of 2,3-dichloroquinoxaline **70** in order to be transformed to macrocycles with two quinoxaline units (Ahmad et al. 1996). The interaction of 5,8-dimethoxy-2,3-dichloroquinoxaline **70b** with the disodium salt of triethylene glycol **84**, prepared by the interaction of triethylene glycol with sodium metal, leads to 2,3,5,6,8,9-hexagydro-12,15-dimethoxy-l,4,7,10-tetraoxocyclododecino[2,3-*b*] quinoxaline **86**. The reactions with monosodium salts of ethylene-, diethylene-, and triethyleglycols **85a–c** result in the podands **87a–c**. In reactions with ethylene glycol **85a,** there occurs the formation of compound **88** as a by-product. The formation of the latter as a sole product takes place when the compound **87a** is treated with sodium hydride in DMSO. The interaction of quinoxaline **70b** with the monosodium salt of triethylene glycol **85c** proceeds more slowly. Even when boiled during 12 h, the main product of the reaction is compound **89** and not podand **87c**.



Scheme 5.17 Synthesis of 1,4-quinoxalinacyclophanes and crown ethers with one and two quinoxaline moieties



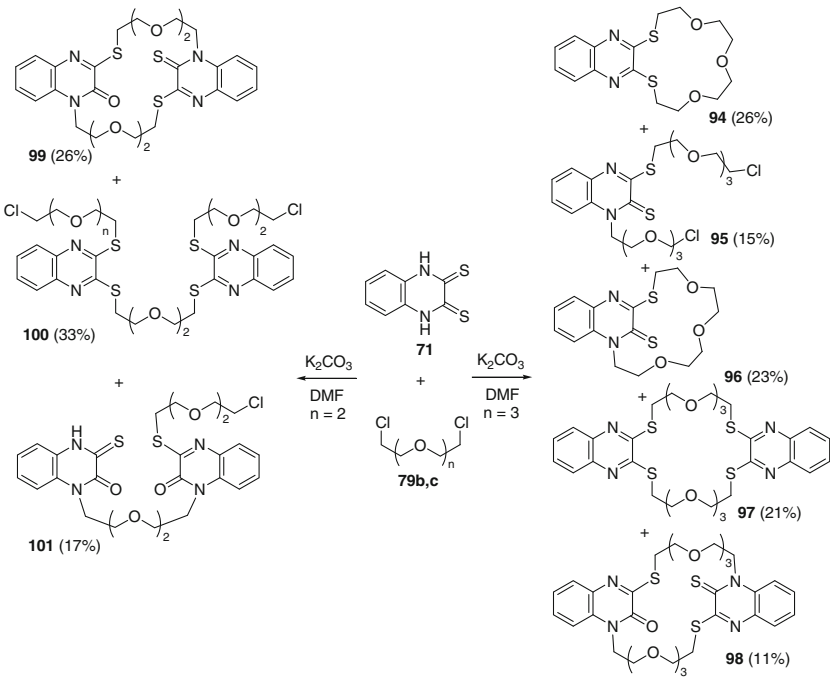
Scheme 5.18 Reactions of 5,8-dimethoxy-2,3-dichloroquinoxaline with the mono- and disodium salts of triethylene glycol in the synthesis of crown ethers with one and two quinoxaline moieties



Scheme 5.19 Reaction of 2,3-dichloroquinoxaline with the *N*,*N*′-(ethane-1,2- and propane-1,3-diyl)bis(2-hydroxybenzamides)

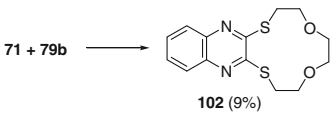
The processing of quinoxaline podands **87b**, **c** with sodium hydride and the subsequent reaction with quinoxaline **70b** in a dilute solution of THF leads to the macrocycles **90** with two quinoxaline fragments. In the case of $n = 1$, the yields are good and in the case of $n = 2$ they are moderate (Ahmad et al. 1996).

Meanwhile, the use of the potassium salts of compounds **91** in the reaction with 2,3-dichloroquinoxaline **70a** in the boiling DMF solution did not lead to the corresponding macrocycles **92**. These reactions resulted in the formation of α,ω-bis



Scheme 5.20 Synthesis of macrocycles containing one or two quinoxaline subcycle units

Scheme 5.21 Reaction of quinoxalin-2,3(1*H*,4*H*)-dithionite with the 1,8-dichloro-3,6-dioxaoctane



[qinoxalino[2,3-*b*]benzoxazepin-13-on-12-yl] alkanes **93** (Scheme 5.19) (Elwahy 2000).

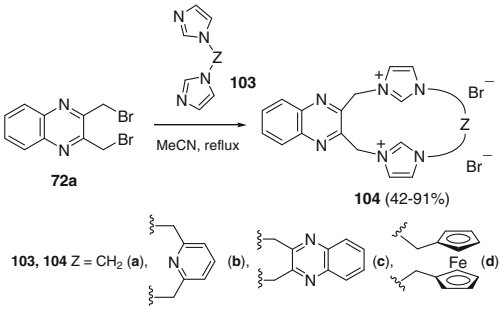
The reaction of quinoxalin-2,3(1*H*,4*H*)-dithione **71** with 1.11-dichloro-3,6,9-trioxaundecane **79c** unlike the reaction of quinoxalin-2,3(1*H*,4*H*)-dione **69** (Scheme 5.17) with the same reagent proceeds with the formation of a mixture of products **94** and **96** (as a result of the interaction of {1 + 1}), **95** (as a result of the interaction of {1 + 2}) and **97**, **98** (as a result of the interaction of {2 + 2}). As can be seen from the Scheme 5.20, four of the five formed compounds are macrocycles. The isomeric structures **94**, **96** and **97**, **98** differ in accordance with the type of the alkylation of quinoxaline systems. When 1,8-dichloro-3,6-dioxaoctane **79b** was used instead of 1,11-dichloro-3,6,9-trioxaundecane **79c** in this reaction, the process proceeded with the formation of the condensation products {2 + 2} only. In this case, the macrocyclic compound **99** contained the two *N*,*S*-alkylated quinoxaline moiety along with the acyclic compounds **100**, **101**; whereas as a result of the interaction of quinoxalin-2,3(1*H*,4*H*)-dithione **71** with 1,5-dichloro-3-oxaoctane **79a** ($n = 0$) only

the acyclic products of the *S*-alkylation of {1 + 2}, {2 + 3}, {3 + 4} and {4 + 5} composition are formed in quantitative yields (Ferfra et al. 2001).

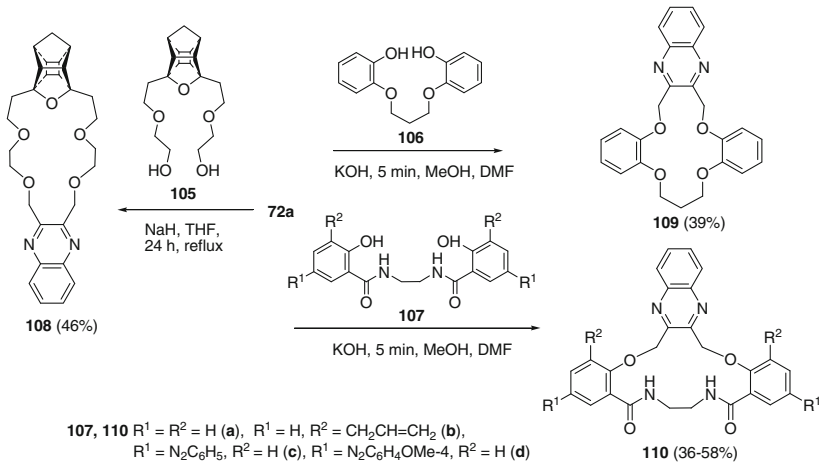
In the case of the interaction of quinoxalin-2,3(1*H*,4*H*)-dithionite **71** with the 1,8-dichloro-3,6-dioxaoctane **79b** it was possible to isolate the macrocycle **102** (Scheme 5.21) (Holzberger et al. 2004).

5.3.2 2,3-Dibromomethylquinoxaline

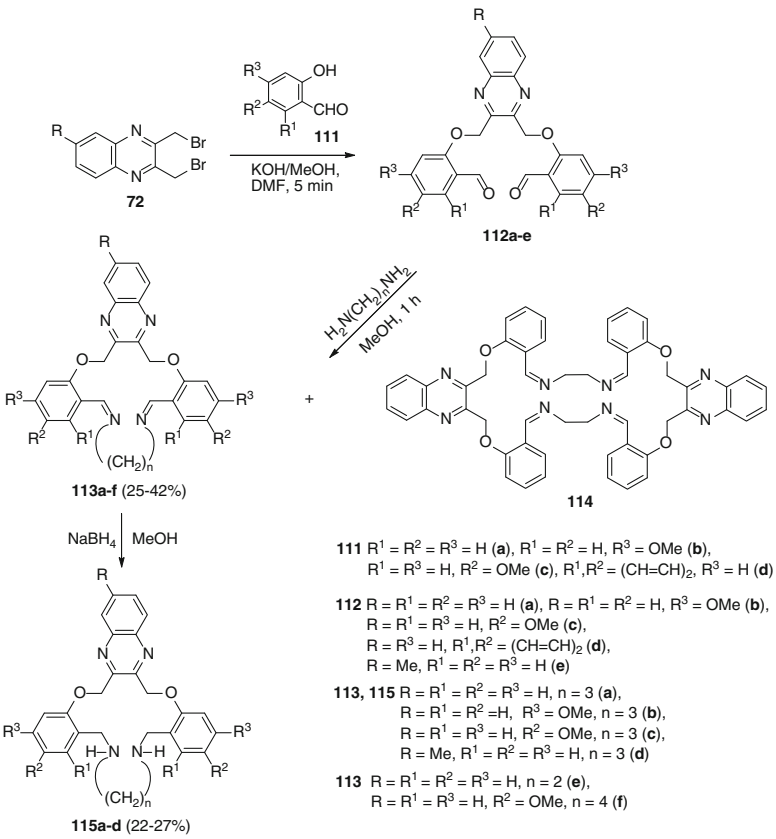
Commercially available 2,3-dibromomethylquinoxaline **72a** was widely used for the synthesis of quinoxaline macrocycles. Its interaction with the 1,1-bis



Scheme 5.22 Reaction of 2,3-dibromomethylquinoxaline with the compounds with two terminal imidazolyl moieties



Scheme 5.23 Reactions of 2,3-dibromomethylquinoxaline with various podands



Scheme 5.24 Reactions of 2,3-dibromomethylquinoxaline with the K-salts of salicylaldehydes in the macrocycles synthesis

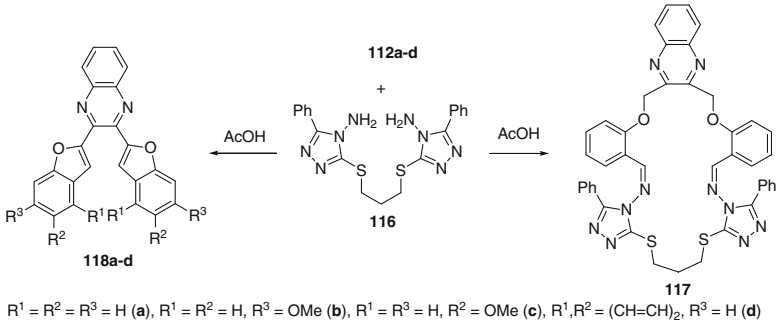
(imidazolyl)methane **103a**, 2,6-bis(imidazolylmethyl)pyridine **103b**, 2,3-bis(imidazolylmethyl)quinoxaline **103c,** and 1,1′-bis(imidazolylmethyl)ferrocene **103d** leads to the quinoxaline macrocycles **104a–d,** respectively, which are fluorescent receptors on anions (Scheme 5.22) (Singh et al. 2007; Niu et al. 2008; Xu et al. 2010).

When the reactions of 2,3-dibromomethylquinoxaline **72a** were carried out with the glycol **105** in THF by heating in the presence of sodium hydride (Sherman et al. 2005) and with diphenols **106** and **107** in DMF in the presence of potassium hydroxide (Elwahy 2000) the analogs of quinoxaline-crown ethers **108–110** were obtained, respectively, (Scheme 5.23).

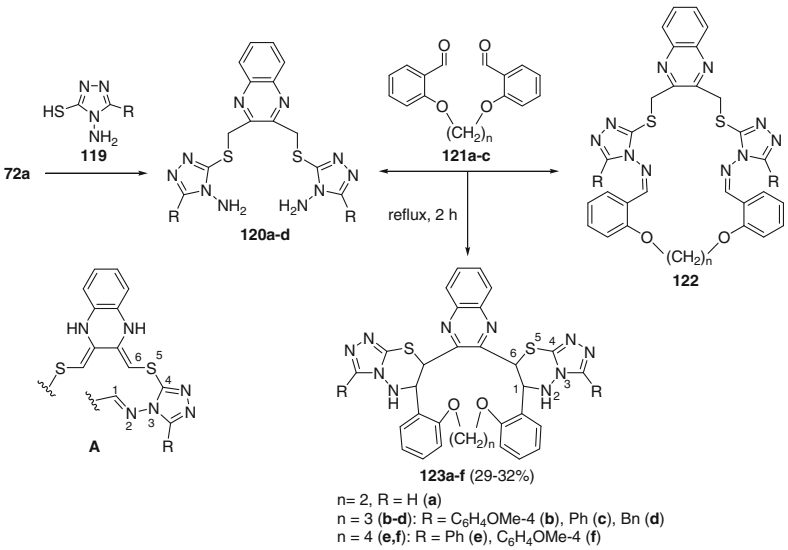
When instead of 2,3-dibromomethylquinoxalines **72** their derivatives **112a–e** were used in the reactions with various bis-nucleophilic reagents, it was further possible to obtain more complex representatives of macrocyclic systems **113–115** with quinoxaline structural blocks (Scheme 5.24). In turn bis(aldehydes) **112a–e** were obtained in 64–73 % yields by the reaction of the K-salt of salicylaldehyde

111a and its derivatives **111b–d** with the 2,3-dibromomethylquinoxalines **72a**, **b** in refluxing DMF. Under high dilution conditions, the reaction of **112a** with diaminoethane in a 1:1 molar ratio in refluxing ethanol failed to give a pure sample of the corresponding Schiff base **113e**. The ^{1}H NMR spectra of the reaction products indicate the presence of a mixture of **113e** and **114** in a 48 % yield. This was also supported by the presence of the characteristic molecular ion peaks in the mass spectrum. All attempts to separate these compounds proved unsuccessful. On the other hand under high dilution conditions, the reaction of **112a** with 1,3-diaminopropane in refluxing ethanol afforded the corresponding macrocyclic Schiff base **113a** in a 27 % yield as the only reaction product. The reduction of the latter with $NaBH_4$ in methanol afforded the corresponding azacrown ether **115a** in a 25 % yield. Similarly, macrocycles **115b–d** were obtained in 22–27 % yields by the $NaBH_4$ reduction of the methanolic solution of the corresponding Schiff bases **113b–d**. The latter were prepared by the cyclocondensation of the appropriate aldehydes **112b–d** with the corresponding diaminoalkanes in 25–42 % yields, respectively. The above conversion was found to be more easily achieved by one-pot synthesis without any isolation of the diimine intermediate. Thus, heating a solution of each of the **112a–c**, **e** in refluxing ethanol for 1 h under high dilution conditions followed by the addition of $NaBH_4$ to the cold reaction mixture, after some work-up afforded the corresponding **115a–d** in 31–34 % yields, respectively (Elwahy 2000).

Under high dilution conditions, the reaction of **112a–d** with **116** in refluxing acetic acid did not lead to the formation of corresponding macrocycles **117**. Instead, the reactions gave 2,3-bis[benzo(*b*)-furan-2-yl]quinoxaline derivatives **118a–d** in 72–83 % yields (Scheme 5.25) (Elwahy 2000). These reactions provided a new and easy access to dibenzofuranylquinoxaline derivatives. The reaction proceeds via intramolecular cyclocondensation of the active methylene with the aldehyde group. The enhanced electrophilicity of C(2) and C(3) in the quinoxaline ring under the acidic condition caused by the protonation of the nitrogen atom activate the methylene group toward the condensation reaction. It is important to mention that



Scheme 5.25 Reaction of bis(aldehydes) **112a–d** with the 1,3-bis(3-phenyl-4-amine-4*H*-1,2,4-triazol-5-sulfanyl)propane **116**



Scheme 5.26 Reaction of 1,2-bis(2-formylphenoxy)alkane with the 1,3-bis(amines)

Sarodnick and co-workers (Sarodnick and Kempter 1991; Sarodnick et al. 1990, 1991) reported the synthesis of some 2-[benzo(*b*)furan-2-yl]quinoxaline derivatives by heating under reflux the corresponding 2-[2-(formylphenoxy)methyl]quinoxalines in the presence of a strong base for 2–3 h in the appropriate solvent.

Bis-nucleophilic **106**, **107**, **116** and bis-electrophilic **112** reagents are the result of the coupling of 4-amino-1,2,4-triazol-3(2*H*)-thione derivatives, salicylic acid, phenols with the dihaloalkanes, and the derivatives of 2,3-dibromomethylquinoxaline **72** with the salicylaldehyde derivatives in various combinations. Changes in the combinations of the initial compounds allowed to synthesize the derivatives of bis (amines) **120** as the bis-nucleophilic reagent and the derivatives of bis(aldehydes) **121** as the bis-electrophilic reagent.

It is interesting to note that under high dilution conditions unlike the above-mentioned bifunctional reagents, the reaction of 1,2-bis(4-amino-1,2,4-triazole-3-ylsulfanylmethyl)quinoxaline **120a** with 1,2-bis(2-formylphenoxy)ethane **121a** (Ibrahim et al. 1994a, b) in refluxing acetic acid did not lead to the formation of the expected macrocyclic Schiff base **122a**. Instead, the reaction gave another product, which could be characterized as the condensed heteromacrocycle **123a** (Scheme 5.26). Similarly, the novel macrocycles **123b–f** were prepared by reacting the appropriate bis(aldehydes) **121a–c** (Ibrahim et al. 1998a, b) with the corresponding bis(amines) **120b–d**.

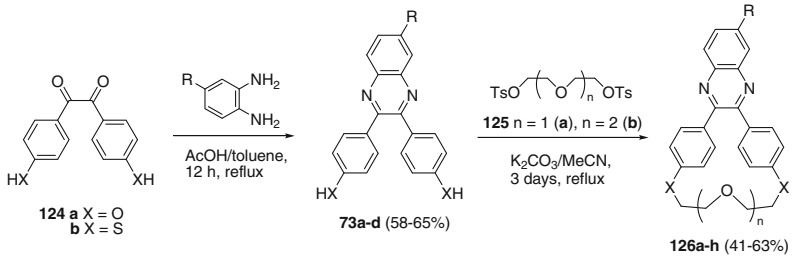
The reaction can proceed via the initial formation of the corresponding macrocyclic Schiff base **122**. Under these reaction conditions, the acid catalyst affords small amounts of the tautomeric methylene form **A**, which could then react with the benzylideneamino carbon as an electrophile to give **123**. The reaction is facilitated

by the enhanced electrophilicity of C(1) caused by the protonation of N(2) under acidic conditions. The reaction can also proceed by an intermolecular *ene*-reaction with the azomethine group as an *ene* part and the *ene*-amine group as an enophile part in the proposed intermediate **A**. In both cases, the formation of the six-membered ring is the driving force for the formation of **123**. It is also expected (Elwahy et al. 2002) that the restricted rotational freedom in the cyclic precursor **122** is due to the rigidity provided by the heterocycles and the aromatic groups. The presence of the two reacting species in close proximity in the same molecule may contribute to the occurrence the intramolecular ring closure of **122** to **123** in a relatively moderate yield (Elwahy et al. 2002).

Thereby, here a new access to the novel condensed heteromacrocycles, which represent an important departure from the traditional heterocyclic chemistry, has been provided.

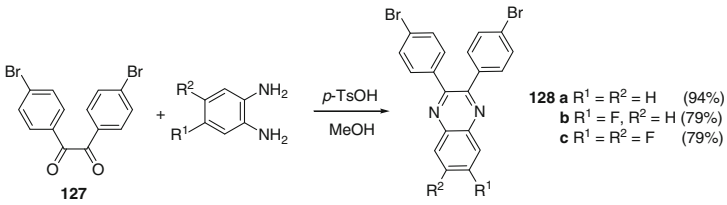
5.3.3 Diphenylquinoxalines

4-[3-(4-Hydroxyphenyl)-2-quinoxalinyl]phenol **73a** and 4-[3-(4-mercaptophenyl)-2-quinoxalinyl]thiophenol **73b** and their derivatives have been easily prepared from commercially available 4,4′-dimethoxybenzil **124a**, **b** using the HBr/AcOH mixture as a demethylating agent (Moylan et al. 1993). They appeared to be convenient structure blockers for the construction of the (2,3-diphenylquinoxaline)-4′,4″-dioxy (4′,4″-dithio)di(trithio)ethylene glycols **126** with selective extraction capabilities regarding alkali and alkali earth metal cations (Scheme 5.27). Compound **124a** is comparatively less reactive than **124b**, since *p*-hydroxy groups have a greater deactivating effect on the electrophilic nature of the carbonyl groups. Therefore, the condensation reaction of **124a** with 1,2-DABs was performed under azeotropic distillation to afford the cyclized products **73**. The latter compounds reacted with ditosylates **125a** and **125b** under high dilution to obtain the crown and thia-crown ethers **126a–h** (Scheme 5.27) (Zamani et al. 2009; Bakavoli et al. 2010).



73 R = H, X = O (**a**), R = H, X = S (**b**), R = Me, X = O (**c**), R = Me, X = S (**d**)
126 R = H, X = O, n = 1 (**a**), R = H, X = O, n = 2 (**b**), R = Me, X = O, n = 1 (**c**), R = Me, X = O, n = 2 (**d**), R = H, X = S, n = 1 (**e**), R = H, X = S, n = 2 (**f**), R = Me, X = S, n = 1 (**g**), R = Me, X = S, n = 2 (**h**)

Scheme 5.27 Synthesis of thia-crown ethers starting from the reaction of 1,2-bis(4-hydroxy- and 4-mercaptophenyl)ethane-1,2-diones with 1,2-DABs

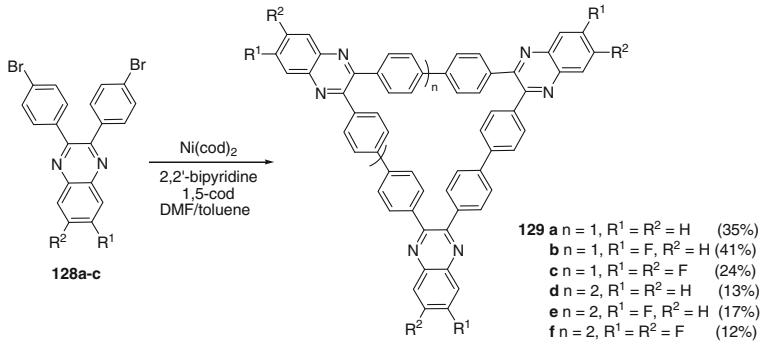


Scheme 5.28 Synthesis of quinoxaline monomers **128**

It has been shown that the crown ether **126a** is a sensing and selective material for the construction of the strontium-PVC (polyvinyl chloride) membrane sensor (Zamani et al. 2009). It should also be pointed out that crown **126a–d** and thia-crown ethers **126e–h** appear prove to be reagents for the selective extraction of alkaline earth over alkali metal ions with 2.7 (Mg^{2+}:Na^{+} extraction ratio) for the crown ether **126b**, whereas this ratio for the thia-crown ether **126f** is 8.0 (Ca^{2+}:K^{+} extraction ratio) (Bakavoli et al. 2010).

A series of fully conjugated quinoxaline-based oligophenylene macrocycles is synthesized by Ni^{0}-mediated Yamamoto-type diaryl homocoupling of (fluorinated) 2,3-bis(4′-bromophenyl)quinoxaline precursors. The "monomers" **128** used in these transformations were prepared in high yields (79–94 %) by acid-mediated condensation between 1,2-bis(4′-bromophenyl)ethane-1,2-dione **127** and the corresponding 1,2-DABs (Marin et al. 2013) (Scheme 5.28). The introduction of fluorine atoms at positions 6 and/or 7 is used as a (proof-of concept) tool for fine-tuning the energy levels (Albrecht et al. 2012; Zhuang et al. 2013; Liu et al. 2014) and allows further elaboration of the final cyclooligomers by nucleophilic aromatic substitution reactions (Charushin et al. 2001; Zhang et al. 2006).

At the monomer stage, the presence of the bromine atoms in the *para* positions of the 2,3-phenyl groups allows to use these derivatives in Ni^{0}-mediated transformations (less toxic and less expensive than the Pd variants). Yamamoto homocoupling of quinoxaline monomers **128** can give rise to cyclic structures and/or polymeric materials (Yamamoto et al. 1992, 1996; Zoombelt et al. 2009; Schwab et al. 2011; Nishiuchi et al. 2012). At first, **128a** was treated with $Ni(cod)_2$ (in the presence of 2,2′-bipyridine and 1,5-cyclooctadiene) in a DMF/toluene mixture and reacted for 3 days at 95 °C [slightly modified compared to the standard conditions used for Ni^{0}-mediated polymerizations (Yamamoto et al. 1992, 1996; Zoombelt et al. 2009; Schwab et al. 2011; Nishiuchi et al. 2012; Marin et al. 2013)]. The resulting crude material was purified by preparative size exclusion chromatography (prep-SEC). Cyclotrimer **129a** [related to the regular *o*,*p*,*p*,*o*,*p*,*p*,*o*,*p*,*p*-nonaphenylene (Meyer and Staab 1969; Rahman et al. 2008)] was isolated as the major product in 35 % yield together with a smaller amount of the analogous cyclotetramer **129d** in 13 % yield, pointing to a bias for the reaction to produce the smallest achievable macrocycles (Scheme 5.29) (Marin et al. 2015). The synthetic protocol was then extended to fluorinated monomers **128b** and **128c**, affording similar results (Scheme 5.29). All macrocycles were obtained in pure form (**129b** and **129e**



Scheme 5.29 Yamamoto cyclooligomerization protocol toward quinoxaline-based cyclic oligoarylenes

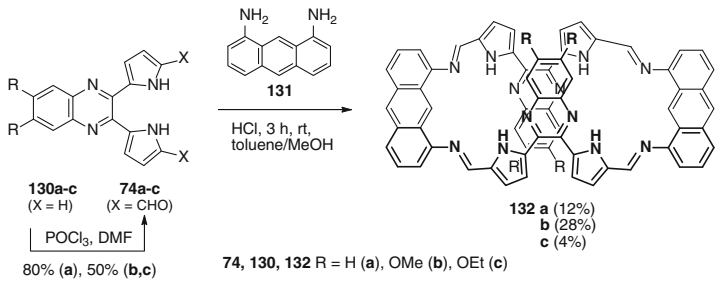
as a mixture of regioisomers) and showed reasonable to good solubility (e.g., in chlorinated organic solvents), allowing full structural characterization. In an effort to increase the macrocycle yield, a high dilution protocol favoring intramolecular cyclization was applied. The obtained results were, however, similar (slightly inferior) to those of the original approach (28 and 7 % yields of **129a** and **129d**, respectively).

These derivatives, after proper extension of the conjugated system and/or variation of the substitution pattern, can be regarded as attractive (complexity-building) molecular platforms toward sophisticated organic architectures that can be applied in materials science, e.g., organic electronics, self-assembly and nanostructure formation, and size-selective supramolecular chemistry [fullerene complexation (Van Rossom et al. 2010; Hirst and Jasti 2012; Rahman et al. 2013) or explosive detection (Rahman et al. 2008; Chen et al. 2010), surface patterning (Mössinger et al. 2010), and conjugated organic frameworks (Guo et al. 2013)].

5.3.4 2,3-Di(pyrrol-2-yl)quinoxalines

In 1999, Sessler and co-workers demonstrated that 2,3-di(pyrrol-2′-yl)quinoxalines (DPQ) constitute an original system for the naked-eye detection of anions (Black et al. 1999). After this pioneering work, the development of various methods for the detection of the anions of a number of dipyrrolylquinoxaline sensor (Black et al. 1999; Anzenbacher et al. 2000; Sessler et al. 2002a, b; Mizuno et al. 2002; Suksai and Tuntulani 2003) were initiated, including the macrocycles (Sessler et al. 2002b; Suksai and Tuntulani 2003).

The quinoxaline-bridged porphyrinoids **132a–c** were prepared from the acid-catalyzed condensation of 1,8-diaminoanthracene **131** with a diformyl-substituted DPQ **74a–c** (Scheme 5.30). The latter intermediates were readily obtained from the DPQ derivatives **130a–c** (Black et al. 1999) by subjecting them to the Vilsmeier



Scheme 5.30 Synthesis of quinoxaline-bridged macrocycles

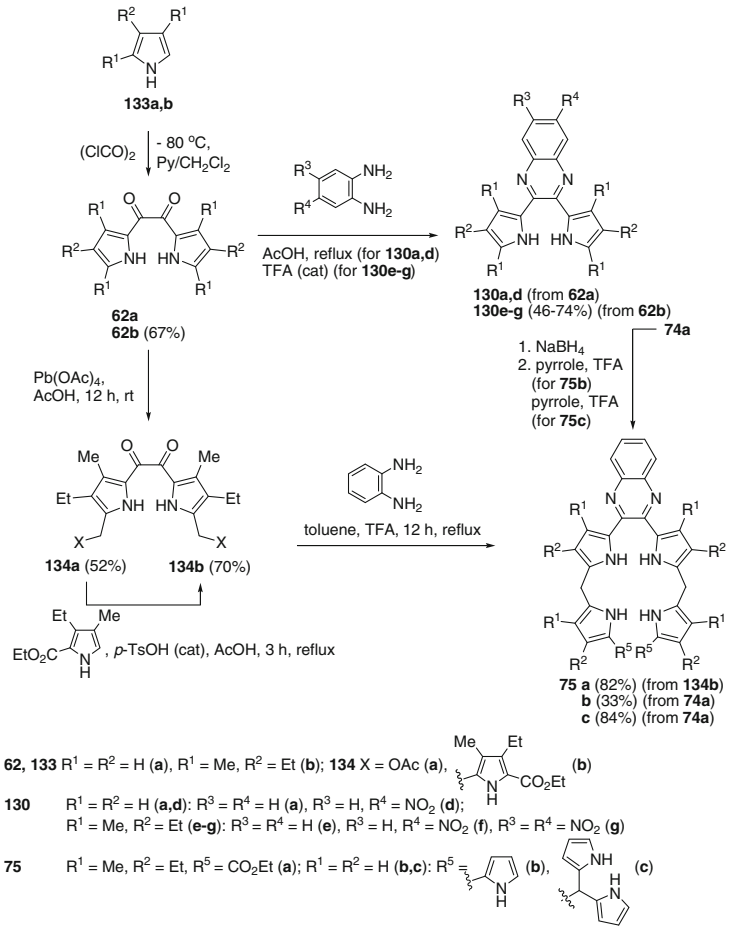
formylation. The orange-colored Schiff base products **132a–c** obtained in this way proved stable to air and moisture, allowing their structures to be assigned by the ^{1}H NMR spectroscopy and high-resolution CIMS analysis. Trace quantities of other condensation products, including linear oligomers and higher order [3 + 3] macrocycles, were observed with the help of the CIMS spectra but could not be isolated in usable quantities. When hydrazine was used instead of 1,8-anthracenediamine in the condensation reaction, the ^{1}H NMR spectroscopic analysis and CIMS studies indicated the formation of a [2 + 2] diaza-bridged macrocyclic product. On the other hand, when 1,2-DAB was used, the analyses indicated the formation of a benzimidazole derivative of **74a–c**. Unfortunately, in neither case could the inferred products be isolated in pure form because of their poor solubility.

It has been shown that macrocycle **132a** could be made to function as an improved fluoride and phosphate anion sensor (Sessler et al. 2002b, 2006; Suksai and Tuntulani 2003).

2,3-Bis(1*H*-pyrrol-2-yl)quinoxalines **130** have been synthesized by the reaction of 1,2-DABs with the dipyrrolyldiketones **62** (Scheme 5.31) obtained according to the improved (by Behr) procedure (Behr et al. 1973) which was first developed for the preparation of the substituent-free dipyrrolyldiketone by Oddo (1911). Condensation of the commercially available derivatives of pyrroles **133a**, **b** with a stoichiometric amount of oxalyl chloride in the presence of dry pyridine afforded the expected diketones **62a**, **b** which were directly isolated from the crude mixture by simply washing with petroleum ether and methanol (Black et al. 1999; Szydlo et al. 2006).

Novel quinoxaline derivatives bearing dipyrromethane or tripyrromethane substituents act as improved anion receptors as compared to the unsubstituted DPQ core from which they are derived. Quinoxaline derivatives **75b**, **c** were synthesized from diformyl-substituted DPQ **74a** (Black et al. 1999) in 33 and 84 % yields, respectively, by treating with $NaBH_4$ followed by TFA and pyrrole in the case of **75b** and TFA and pyrrole in the case of **75c** (Sessler et al. 2002a). However no macrocyclization of the compounds **75b**, **c** had been achieved (Scheme 5.31).

The remarkable potential of the quinoxaline moiety for the preparation of macrocyclic structures with extended π-conjugated systems has proved of interest in

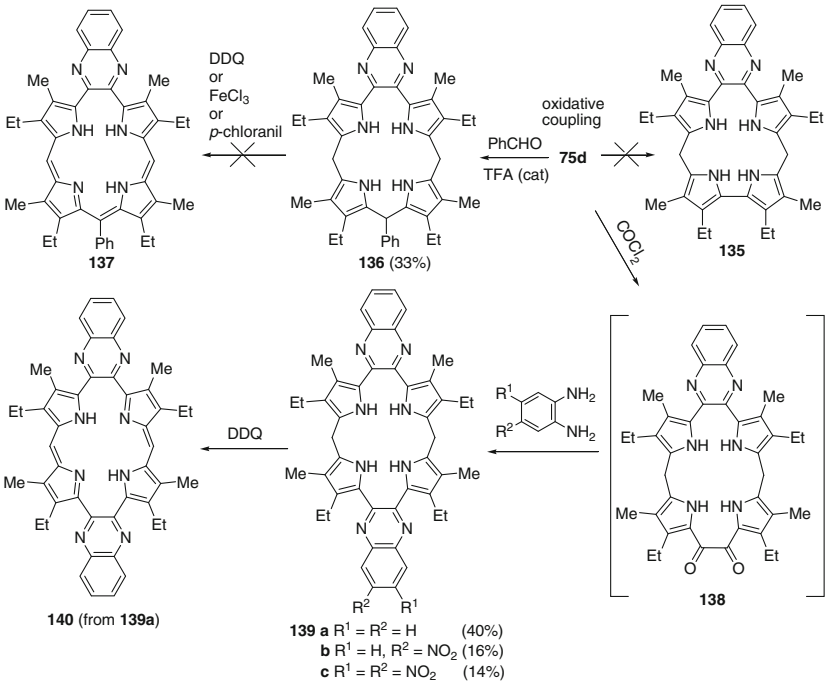


Scheme 5.31 Synthesi of acyclic di- and tetrapyrrolylquinoxalines from dipyrrolyldiketones

the development of quinoxaline-containing expanded porphyrins. To this end, a synthetic strategy has been developed based on the use of kryptopyrrole **133b** for the preparation of highly soluble and easy-to-functionalize polypyrrolic quinoxalines.

According to the procedure described by Oddo (1911) the soluble peralkyl dipyrrolyldiketone **62b** in a 67 % yield had been prepared (Szydlo et al. 2004). Further, **62b** was converted to the corresponding peralkyl DPQs **130e–g** with an excess of diamine in refluxing toluene and in the presence of a catalytic amount of trifluoroacetic acid.

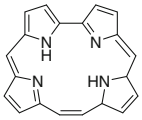
As the direct functionalization of **130e–g** failed, the precursor **62b** was converted to the corresponding diacetoxymethyl derivative **134a** with $Pb(OAc)_4$ in acetic acid in a 52 % yield (Scheme 5.31). The latter then reacted with ethyl

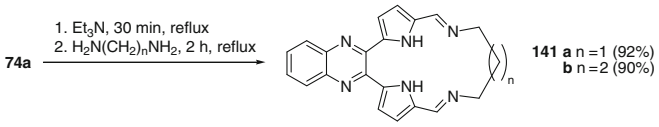


Scheme 5.32 Synthesis of tetrapyrrolic macrocycles

3-ethyl-4-methyl-1*H*-pyrrole-2-carboxylate, affording the diester-protected tetrapyrrolyldiketone **134b** in a 70 % yield (Scheme 5.31). Finally, the tetrapyrrolylquinoxaline (TPQ) **134b** was obtained using a mild procedure established for the preparation of **75a** in a 82 % yield. The subsequent saponification/decarboxylation sequence with NaOH in refluxing ethylene glycol afforded the bis-R-free TPQ **75d** (R^1 = Me, R^2 = Et, R^5 = H) quantitatively. Thus starting from the commercially available kryptopyrrole, the key intermediate **75b** was efficiently prepared in five steps and a 21 % overall yield (Szydlo et al. 2006). The unique quinoxaline-containing macrocycle precursor **75d** has been subjected to different ring closing options. A different oxidative macrocyclization via a direct pyrrole-pyrrole *ortho*-bond coupling–whether metal-templated or not–did not afford any quinoxaline-containing corrphycene[2] **135** (Scheme 5.32). Considering that the quinoxaline moiety may prevent the system from adopting a suitable conformation for a direct ring closing, it was decided to perform a ring closure with additional

[2]Corrphycene is structural isomer of porphyrine (Sessler et al. 1994).



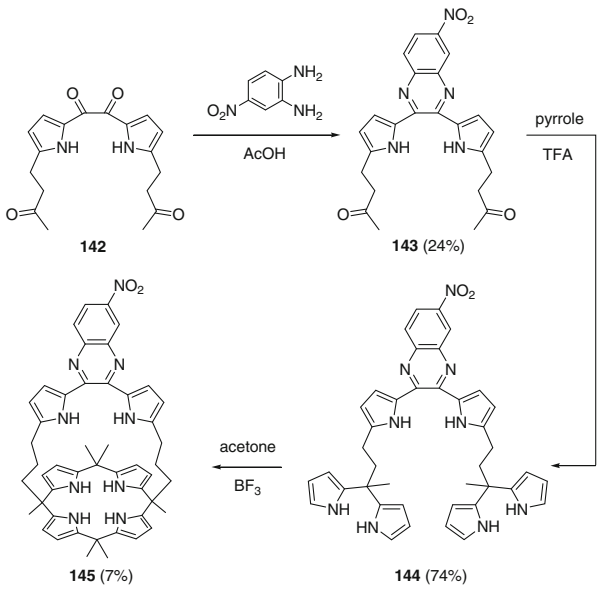


Scheme 5.33 Synthesis of ligands 2,3-bis(pyrrol-2′-yl)quinoxaline frame

meso carbon atoms. To this end, in parallel the reaction of bis-R-free TPQ **75d** with stoichiometric amounts of benzaldehyde or oxalyl chloride were carried out. Both approaches were successful. The condensation of **75d** with benzaldehyde afforded the (2.1.1.1) quinoxaline-containing porphyrinogen **136** in a 33 % yield (Scheme 5.32). On the other hand, the preparation of a bis-quinoxaline macrocycle appeared remarkably efficient. Indeed, not only did the equimolar condensation of oxalyl chloride with **75d** afford the expected diketone, but the subsequent condensation of the crude diketone with excess 1,2-DAB provided the bisquinoxaline porphyrinogen **139a** in a 40 % overall yield (Scheme 5.32). Ultimately, it was efficiently oxidized using excess DDQ in CH_2Cl_2 at room temperature, affording the unprecedented (2.1.2.1) tetrapyrrolic macrocycle **140**. The crude diketone **138** was also condensed with 4-nitro- or 4,5-dinitro-1,2-DABs to afford the nitro-functionalized analogs **139b**, **c** in 16 and 14 % overall yields, respectively (Szydlo et al. 2006). It should be pointed out that unlike the macrocycle **139,** the oxidation of porfirinogen **136** to the corresponding tetrapyrrolic macrocycle **137** did not as yet occur with the DDQ, *p*-chloranil, or $FeCl_3$ (Szydlo et al. 2006). The antiaromatic analogs of the calix[4]phyrins (Kral et al. 2000) macrocycles **140** appeared a good ligand for most of the metals tested. In particular, they were shown to form stable complexes with the first row metals, such as Zn and Cu, or the larger ones, such as Pd, Cd, Sn, or Pb (Szydlo et al. 2006).

The interaction of the 2,3-bis(5′-formylpyrrol-2′-yl)quinoxaline **74a** easily obtainable from 1,2-bis(1*H*-pyrrol-2-yl)ethane-1,2-dione **62a** via 2,3-bis(1*H*-pyrrol-2-yl)quinoxaline **130a**, with equimolar amounts of 1,3-diaminopropane (or 1,4-diaminobutane) in boiling methanol with triethylamine form the macrocycles **141a**, **b** (Scheme 5.33). Both compounds display selective and sensitive fluorescence quenching responses toward Hg^{2+} ion in aqueous solution (Wang et al. 2005a, b).

New calix[4]pyrroles **145** bearing dipyrrolylquinoxaline as strapping elements have been synthesized (Kim et al. 2009). The synthesis of receptor **145** starts with ketone **142**, a species that was prepared by the reaction of oxalyl chloride with 2 equivalents of 2-(3-oxobutyl)pyrrole (Yadav et al. 2001). Once in hand, **142** was reacted with 4-nitro-1,2-DAB in the presence of acid to afford bisketone **143** in 24 % yield (Black et al. 1999; Anzenbacher et al. 2000). Treatment of this latter intermediate with neat pyrrole in the presence of trifluoroacetic acid afforded the bis-dipyrromethane **144** in 74 % yield (Scheme 5.34). While this procedure proved effective, attempts to effect the direct alkylation of 6-nitro-2,3-di(2′-pyrrolyl)quinoxaline with methyl vinyl ketone produced only trace quantities of the desired product **144**. Acid-catalyzed condensation of **144** with acetone then gave the



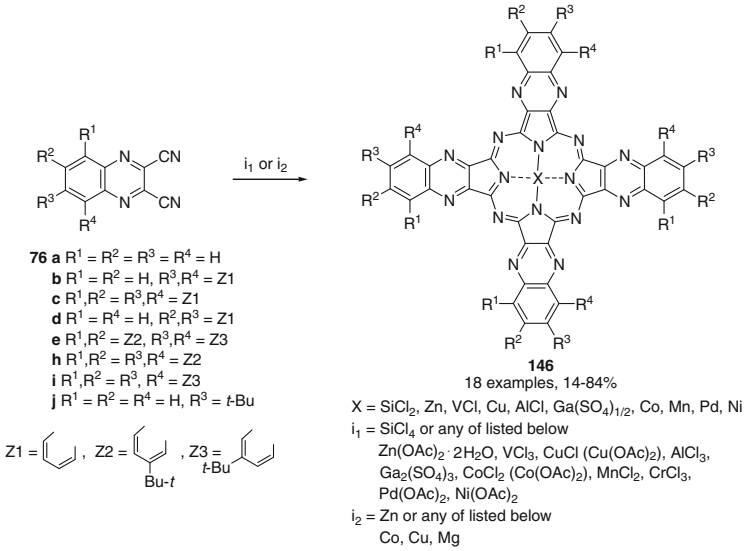
Scheme 5.34 The synthesis of 6-nitro-dipyrrolylquinoxaline-strapped calix[4]pyrrole **145**

desired strapped calix[4]pyrroles **145** in 7 % yield. Support for the proposed structures was obtained from NMR spectroscopic and high-resolution mass spectrometric analyses.

The binding behavior of these receptors at 25 °C was investigated first by proton NMR spectroscopy in CD_3CN/DMSO-d_6 (9:1 v/v), as well as by UV-vis spectroscopy and isothermal titration calorimetry in MeCN/DMSO (97:3, v/v). The receptors displayed a selective colorimetric response when exposed to the fluoride, dihydrogen phosphate, and acetate anions (studied in the form of the corresponding tetrabutylammonium salts) and an enhanced affinity as compared to a comparable calix[4]pyrrole system lacking the dipyrrolylquinoxaline-containing strap.

5.3.5 2,3- and 6,7-Dicyanoquinoxalines

At first the unsubstituted metal-free quinoxalinoporphinazine **146** ($R^1 = R^2 = R^3 = R^4 = H$, X = HH) was obtained in a 67 % yield by heating dinitrile quinoxaline-2,3-dicarboxylic acid in benzyl alcohol and chlorobenzene at 180 °C with metallic lithium followed by the treatment of the resulting complex with dilute hydrochloric acid (Gal'pern and Luk'yanets 1969) (Scheme 5.35). A higher yield of **146** ($R^1 = R^2 = R^3 = R^4 = H$, X = HH) (95 %) is achieved when carried out in fusion with sodium hydroxide at 220 °C within 15 min (Korzhenevskii et al. 2006). Metal-free benzo[*g*]quinoxalinoporphinazine **146** ($R^1 = R^4 = H$, R^2, R^3 = Z1, X = HH) obtained from **76d** as a result of processing sodium pentoxide and



Scheme 5.35 Synthesis of quinoxalinoporphinazines and complexes

demetallization was followed by concentrated sulfuric acid (Freyer 1994). Pentanol was the solvent for obtaining the magnesium complex **146** (R^1 = R^4 = H, R^2, R^3 = Z1, X = Mg) when heating **76d** and magnesium powder (Freyer 1994).

One of the methods of preparing metal quinoxalinoporphinazines involves the thermolysis of quinoxaline **76a** with dry manganese and chromium chlorides at 220 °C, which leads to **146** (R^1 = R^2 = R^3 = R^4 = H, X = Mn, Cr, Cl) in 80–84 % yields (Smirnova et al. 1996, 1997). Similarly, heating quinoxaline **76j** with the acetates of zinc, cobalt, or copper at 220 °C without any solvent, but in the presence of ammonium molybdate as a catalyst resulted in corresponding metal complexes of the macrocycles **146** (R^1 = R^2 = R^4 = H, R^3 = *t*-Bu, X = Zn, Co, Cu) in 57–74 % yields (Efimova et al. 2008).

Other methods involve the use of high boiling solvents. Heating quinoxalinodinitrile **76a** and benzo[*g*]quinoxalinedinitrile **76d** in trichlorobenzene in the presence of metals or their chlorides leads to **146** (R^1 = R^4 = H, R^2 = R^3 = H, R^2, R^3 = Z1, X = Zn, Co, Cu, Ni, Pd, VCl) (Gal'pern et al. 1968, 1969, 1971; Freyer 1994). Comparison of the electronic absorption spectra of the tetra-benzo[*g*] quinoxalino-2,3-porphyrazines complexes synthesized in quinoline, dimethylsulfoxide with spectra of the corresponding tetra-2,3-pyrazino- and tetra-2,3-quinoxalinoporphyrazines in the same solvents makes it possible to draw the following conclusion. In a number of metal complexes of octaazaphthalocyanines, the consecutive linear annulation of benzene rings which does not change the symmetry of the molecule leads to a bathochromic shift of the long-wavelength absorption band. The magnitude of this displacement upon transition from one group of compounds to another is 1500–1800 cm^{-1} (Gal'pern and Luk'yanets

1971). Quinoline is an especially popular solvent, used for the first time for the synthesis of quinoxalinoporphyrazines in 1968. The method of synthesis in quinoline in the presence of urea and tributylamine gained further popularity.

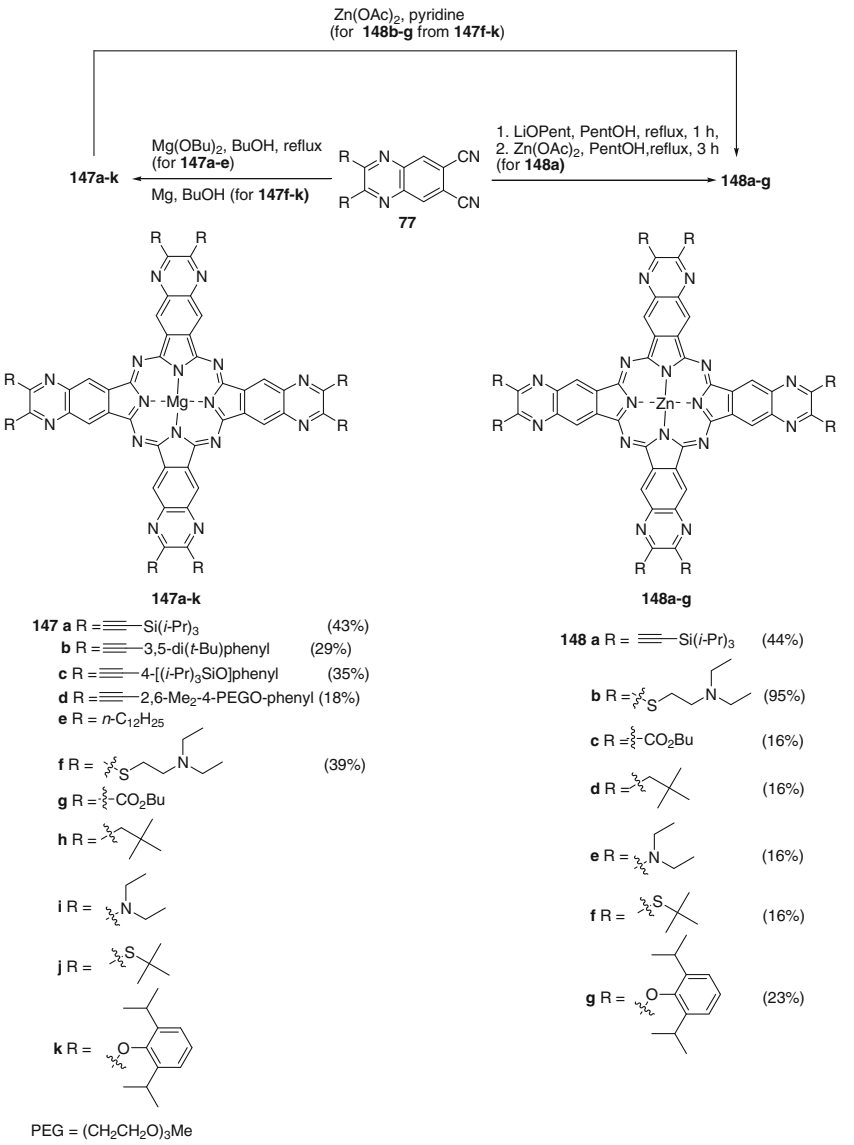
The dichlorosilicon complexes of substituted tetra-2,3-pyrazinoporphyrazines were obtained via the condensation of 2,3-dicyanoquinoxaline **76a**, 2,3-dicyano-benzo[*f*]quinoxaline **76b** and 2,3-dicyano-dibenzol[*f*,*h*]quinoxaline **76c** with silicon tetrachloride in the presence of urea, quinoline, and tri-*n*-butylamine. The hydrolysis of the Si-C(1) bond in concentrated H_2S0_4, followed by 0.01 N NaOH and aqueous NH, afforded the corresponding dihydroxides, which were converted to the bis(tri-*n*-hexylsiloxy)silicon derivatives via tri(*n*-hexy1)silane in 3-picoline (2,4,6-collidine) and tri-*n*-butylamine. The axial tri-*n*-hexylsiloxy substituents at the central silicon atom prevent aggregation in organic solvents, permitting detailed studies on the effects of structural modifications on the electronic spectra of tetraazaphthalocyanines. Each benzo ring addition, angularly condensed to the tetra[2,3]quinoxalinoporphyrazine, induces a hypsochromic shift (−10–15 nm) of the main absorption maximum (Yanagi et al. 1994; Kudrevich and van Lier 1996).

When **76d–i** were heated in quinoline with various organic (acetate of zinc) or inorganic (chlorides of other metals) salts in the presence of urea and tributylamine the zinc, vanadium, copper, aluminum, cobalt complexes **146** have been obtained (Kudrevich et al. 1996).

The synthesis of tetra[6,7]quinoxalinoporphyrazines **147**, **148** in which pyrrole rings had been annulated to benzene instead of pyrazine rings as shown above on examples **77** (Scheme 5.36). This involves the initiated magnesium butoxide cyclization of the corresponding precursors **77** followed by the demetallation by *p*-toluenesulfonic acid and the subsequent chelation of zinc into the center of the metal-free macrocycle using anhydrous zinc acetate. This is the best approach to **148c–g** (Novakova et al. 2010). Other procedures with lithium butoxide as an initiator or employing the template effect of zinc cation Zn^{2+} in high boiling solvents (DMF, DMAE, and quinoline) did not lead to better results. The magnesium butoxide method was also successful in the preparation of **148e**, although previous attempts did not lead to desired product (Musil et al. 2007a).

Acetylene derivatives of [6,7]quinoxalinoporphyrazines **147a–d**, of interest as photosensitizer for photodynamic therapy have been obtained (Faust 2001; Mitzel et al. 2001, 2003). For imparting water solubility the zinc complex was synthesized from **148b** with the 4 diethylamino fragments which are readily alkylated with ethyl iodide to form quinoxalinoporphyrazine with eight quaternized nitrogen atoms (Zimcik et al. 2010).

Equimolar molar amounts of 6,7-dicyano-2,3-diethylaminoquinoxaline **77** (R = NEt_2) and 5,6-dicyano-2,3-diethilaminopyrazine in refluxing butanol and more than tenfold metallic lithium for 3 h gives the six possible porphyrazines **149–154** (Musil et al. 2007a) (Fig. 5.8).



Scheme 5.36 Synthesis of tetra[6,7]quinoxalinoporphyrazines

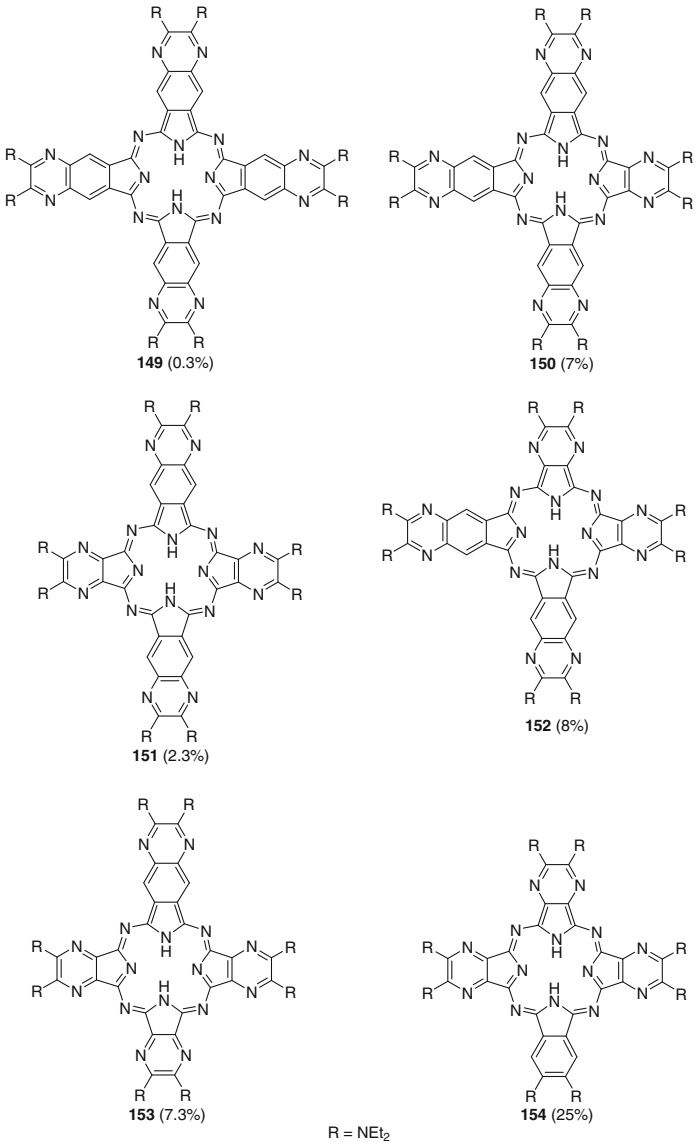
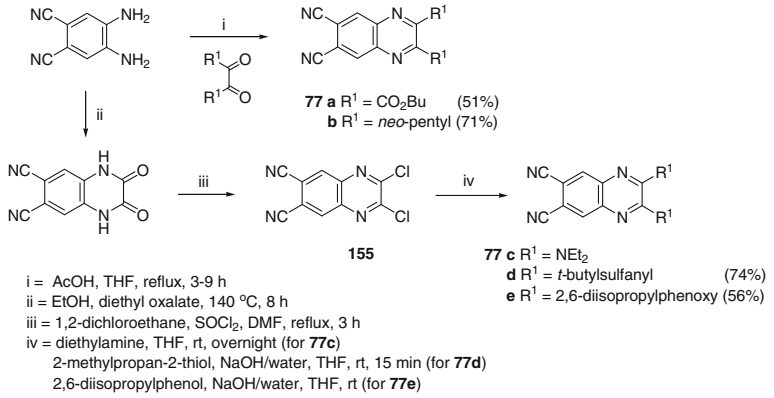


Fig. 5.8 Porphyrazines with one-, two-, three-, four-quinoxaline, and pyrazine moieties



Scheme 5.37 Synthesis of precursors for the synthsesizing of porphyrazines

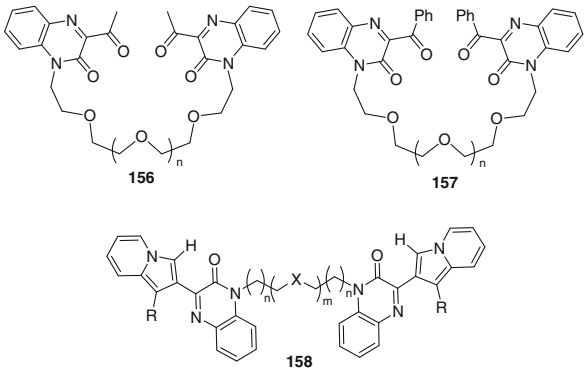


Fig. 5.9 1,*n*-Bis (quinoxalin-1-yl)alkanes–precursors of the quinoxaline macrocycles

The synthesis of the precursors **77a–e** was carried out via two different approaches (Scheme 5.37). In method A **77a**, **b** with their substituents connected through the C–C bond were prepared by condensing 4,5-dicyano-1,2-DAB with appropriately substituted vicinal diketones prepared similarly to the procedures (Babudri et al. 1995; Musil et al. 2007b). Acid was used as a solvent. In method B, the recently developed intermediate 2,3-dichloroquinoxaline-6,7-dicarbonitrile **155** (Musil et al. 2007b) was used for the synthesis of the heteroatom-linked peripheral chain bearing precursors **77c–e**. The chlorine atoms on the electron-deficient positions of **155** are easily substituted by nucleophilic amines to **77c**. Under mild conditions the thiolates and phenolates as the stronger nucleophiles rapidly reacted with **155** to yield the precursors **77d** and **77e**, in good yields, respectively.

5.4 1,*n*-Bis(quinoxalin-1-yl)alkanes in the Synthesis of Macrocycles

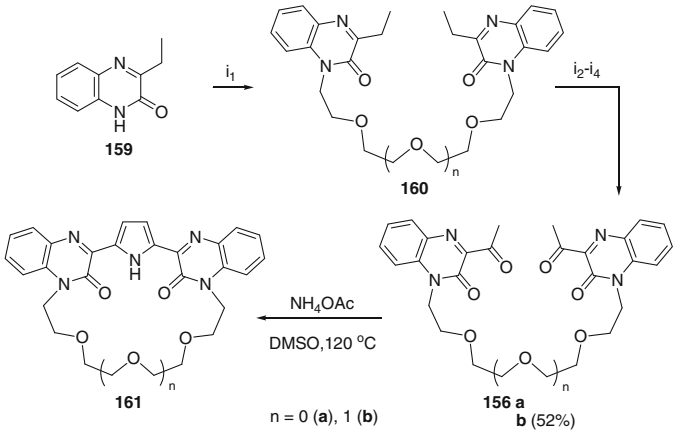
The third approach to the synthesis of macrocycles based on quinoxaline podands terminated quinoxaline fragments with functional groups capable of accomplishing the closure of the macrocycle by interacting with other reagents. 1,*n*-Bis (3-acetylquinoxalin-2-on-1-yl)alkanes **156**, 1,*n*-bis(3-benzoylquinoxalin-2-on-1-yl) alkanes **157**, 1,*n*-bis(3-indolizinylqinoxalin-2-on-1-yl)alkanes **158** were used. Here two quinoxaline moieties are attached to the nitrogen atoms of amide groups having different length and nature of the spacers. The amide carbonyl groups remain unaffected in the composition of the newly formed quinoxaline podands **156–158** (Fig. 5.9). When necessary, they can play an important role in complex formation. The presence of acetyl and benzoyl functions in position 3, i.e, in the α-position to the imino carbon atom of the quinoxaline system can further promote carrying out various reactions with the participation of these functional groups, with the formation of a new heterocyclic system which can be introduced as a substituent through the C–C bond or as an annulated heterocycle forming the general C–N bond. The presence of excess π-electron indolizine makes it possible to carry out the oxidative C–C coupling at the 3,3′ positions of the indolizine. These opportunities, in turn, allow the synthesis of a wide range of macrocycles (Mamedov et al. 2007, 2013a, b; Kalinin et al. 2009).

Unlike the synthesis of quinoxaline macrocycles based on the macrocycles and quinoxalines in which the quinoxaline is only or predominantly connected by atoms of C(2) and C(3), refortal in (Mamedov et al. 2007, 2009a, b, 2013a, b; Kalinin et al. 2009) other methods of synthesis of macrocycles have been developed in which the quinoxaline is connected by the atoms of N(1) and C(3). In the only known work (Ferfra et al. 2001), the synthesis of the latter types of macrocycles was achieved by the interaction of quinoxaline-2,3-dithione with the dichlorooxaalkanes, which allowed the synthesize of their single representatives, depending on the length of dichlorooxaalkanes. Different types of macrocycles were obtained, and sometimes the reaction did not lead to any macrocycle.

*5.4.1 1,*n*-Bis(3-acetylquinoxalin-2-on-1-yl)alkanes*

The interaction of quinoxalinepodands **156** (Kalinin et al. 2007; Kalinin and Mamedov 2014) with the acetyl moieties and ammonium acetate when heated in DMSO leads to the formation of the macrocyclic system. The process was accompanied by the formation of the pyrrole ring of **161** from the acetyl fragments of **156** and ammonia. The reaction was carried out in highly diluted mixtures in the presence of $MgSO_4$, capable of binding water and serving as a template for the synthesis of macrocycles which increases the yields of the cyclophanes **161** from 8–10 to 22–24 % (Table 5.1) (Kalinin and Mamedov 2014).

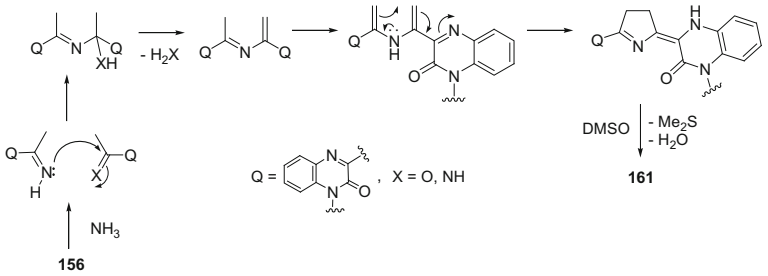
Table 5.1 Yields of compounds **161**



i_1 = $Br(CH_2CH_2OCH_2(CH_2OCH_2)_nCH_2OCH_2CH_2Br$, KOH, dioxane, 8 h, reflux
i_2 = Br_2, dioxane, 12-15 °C, 2 h, then rt, 3 h
i_3 = NaN_3, DMSO, 24 h, rt
i_4 = 90% AcOH, 4.5 h, 80 °C

Entry	**156**	n	Product (Yield, %)
1	**156a**	0	**161a** (8[a], 24[b])
2	**156b**	1	**161b** (10[a], 20[b], 22[c])

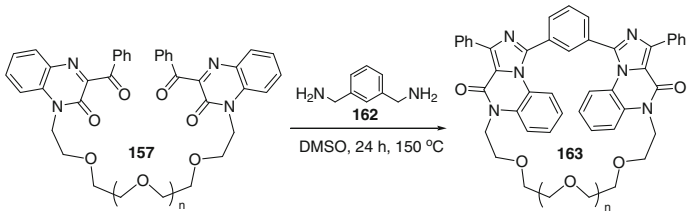
[a] without high dilution
[b] in the presence of $MgSO_4$
[c] in the presence of $MgSO_4$ + with high dilution



Scheme 5.38 Plausible mechanism for the formation of the pyrrole ring

The key step of the above process, i.e., the formation of the pyrrole ring with closure of the macrocycle apparently proceeds in accordance with the Scheme 5.38.

Table 5.2 The synthesis of diimidazoquinoxalinabenzenecyclophanes **163a–c**



Entry	Diketone	n	Product (Yield, %)[a]
1	**157a**	0	**163a(I)**[f] (5[b], 8[c]), **163a(II)**[f] (4[b], 6[c])
2	**157b**	1	**163b(I)**[f] **+ 163b(II)**[f] (8[b,c], 14[d], 11[e])
3	**157c**	2	**163c** (8[b], 11[e])

[a]After solvent evaporation, the residue was purified by a short gel plug using CH_2Cl_2 as an eluent and then recrystallized from the corresponding solvent.
[b] Without a template.
[c-e] In the presence of [c]Li^+, [d]Na^+ and [e]K^+ as templates.
[f]In the cases of n = 0, 1 the reactions proceed with the formation of atropisomers (**I**,**II**).

The precursors of cyclophanes **161,** i.e., podands **156** were prepared in four steps starting from 3-ethylquinoxalin-2-one **159** (Mamedov et al. 2005a; Kalinin and Mamedov 2009), the alkylation of which with dibromooxoalkanes leads to **160** with ethyl moieties. The transformation of ethyl acetyl fragments was accomplished in three stages: bromination, the substitution of the bromine atom by the azide group, and conversion of azidoethyl fragments into acetyl function when heated in aqueous acetic acid.

*5.4.2 1,*n*-Bis(3-benzoylquinoxalin-2-on-1-yl)alkanes*

The original methods for the synthesis of macrocycles **163** with two imidazoquinoxaline blocks based on the 1,*n*-bis(3-benzoylquinoxalin-2-on-1-yl)alkanes **157** have been developed (Mamedov et al. 2009a). Its application to the synthesis of imidazo[1,5-*a*]quinoxalin-4-ones (Mamedov et al. 2004a, 2009a; Kalinin and Mamedov 2008b; Kalinin et al. 2013) based on the interaction of 3-benzoylquinoxalin-2(1*H*)-one with benzylamine to the 1,*n*-bis (3-benzoylquinoxalin-2-on-1-yl)alkanes **157** and *m*-xylylenediamine **162** makes it possible to synthesize macrocyclic compounds–diimidazoquinoxalinabenzenecyclophanes **163** in 5–8 % yields (Table 5.2). The use of $LiClO_4$, NaCl, and KI as templates affects the yield of macrocycles in the interactions of diketones **157** with *m*-xylylenediamine **162** in a different way. While the presence of Li^+ has virtually no effect on the yields of the formation of macrocycle **163b**, which in this case is 8 %, the yields in the presence of Na^+ increase twofold and become 14 %. Further

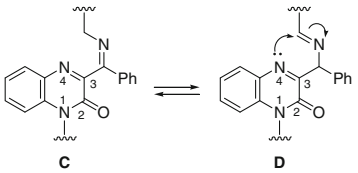


Fig. 5.10 Plausible mechanism for the formation of the imidazoannulation

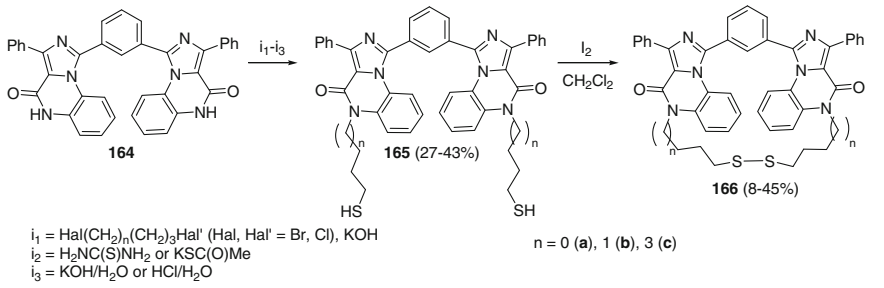
increase of the cation size leads to the reduction of the yields by 11 %. High dilution does not increase the yields of the macrocycles **163**. The use of AcOH instead of DMSO leads to the formation of **163b** with a 7 % yield. The purification of compounds **163** was performed by column chromatography with subsequent recrystallization. The mixture when preprocessed was treated with the hydrochloride of semicarbazone for 3 h in boiling AcOH, which greatly facilitated the separation of the products.

Compound **163a** was obtained as a mixture of two diastereomers (ca. 1:1), which were separated and characterized separately (Mamedov et al. 2009b). Presumably these diastereomers (conformers) are due to the different (*syn* and *anti*) mutual orientation of the tricyclic systems.

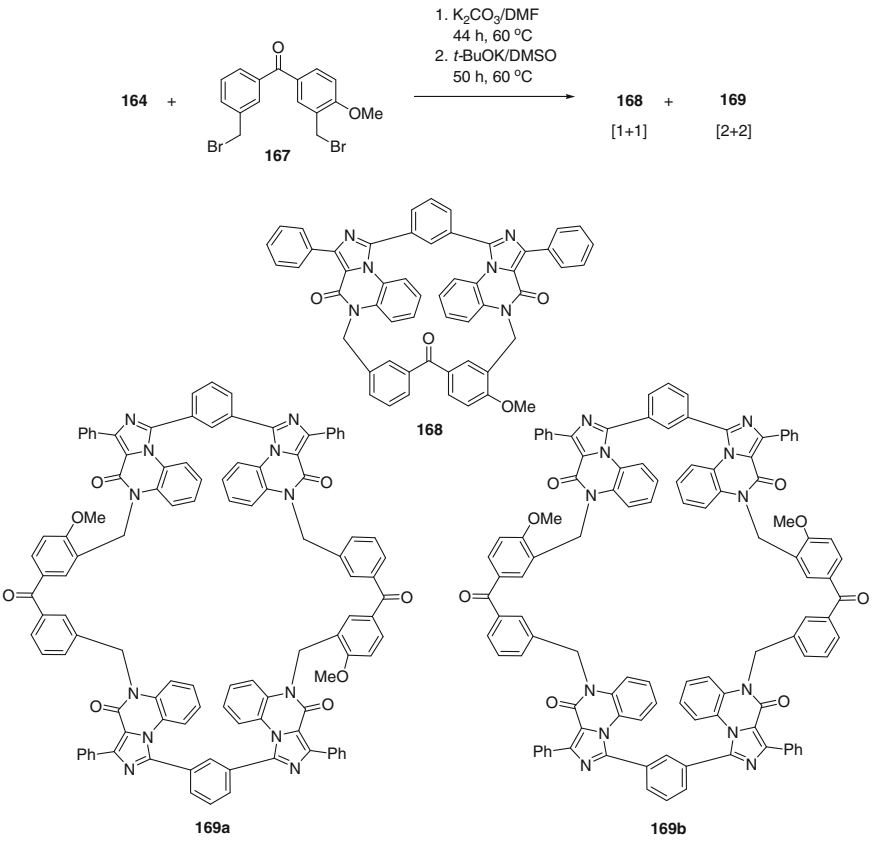
The formation of imidazoquinoxalines apparently proceeds through the tautomeric form **D** formed at the first stage of the reaction of the bases of Schiff **C** in which nucleophilic attack of atom N(4) on the imine atom of carbon occurs with the closure of the imidazoline cycle the aromatization of which when exposed to the DMSO or oxygen of the air leads to the imidazo[1,5-*a*]quinoxalin-4-one derivatives (Fig. 5.10).

The imidazoannulation of 3-benzoylquinoxalin-2-ones has been widely studied on various ketones of quinoxalines in their reactions with compounds containing an aminomethyl moiety (benzylamine picolylamine, *m*-xylylenediamine), that allowed the creation a "library" of imidazo[1,5-*a*]quinoxalines with substituents at different positions (Mamedov et al. 2004a, 2009b, 2008a, b; Kalinin et al. 2013).

A method of synthesis of the imidazoquinoxalinacyclophanes containing a disulfide moiety in the spacer has been developed based on **164**. Molecular iodine was used to close 1,3-bis[5-(3-mercaptoalkyl-1)-3-phenylimidazo[1,5-*a*]quinoxalin-4-one-1-yl]benzenes **165** to the macrocycle **166** (Scheme 5.39). The



Scheme 5.39 Synthesis of macrocyclic disulfides starting with *m*-bis(3-phenylimidazo[1,5-*a*]quinoxalin-4(5*H*)-on-1-yl)benzene



Scheme 5.40 Synthesis of macrocycles with one- and two *m*-bis(3-phenylimidazo[1,5-*a*] quinoxalin-4(5*H*)-on-1-yl)benzene frames

longer the alkyl chain in **165a–c**, the higher the yield of macrocyclic disulfides **166a–c** which were 8, 30 and 45 %, respectively, with closure of bismerkaptanes **165** with propylene, butylene, and hexylene fragments. The reactions were carried out in a highly dilute solution of methylene chloride at room temperature (Mamedov et al. 2009a). The introduction of haloalkyl fragments in **164** was achieved either in one stage of the alkylation by dihaloalkanes or in two stages, i.e, the alkylation by halo-alcohols and the subsequent substitution of the hydroxyl group by halogen. The transformation of haloalkyl derivatives into the mercaptoalkyl derivatives of 1,3-bis (3-phenylimidazo[1,5-*a*]quinoxalin-4-on-1-yl)benzene was achieved in two well-known ways: with thiourea followed by the alkaline hydrolysis of the isothiouronium salts and with thioacetate potassium and the subsequent acid hydrolysis or the hydrazinolysis of thioacetate with potassium thioacetate followed by the acidic hydrolysis or hydrazinolysis of the thioacetate (Mamedov et al. 2009a).

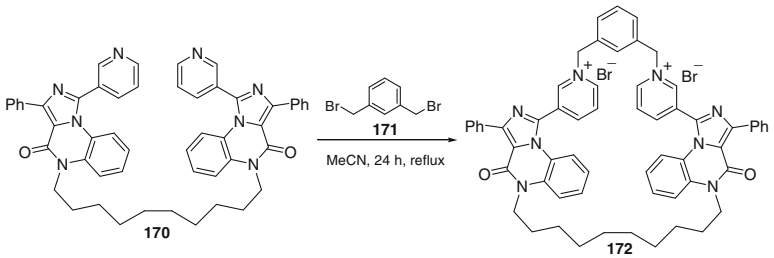
In a continuation of their work, the authors (Mamedov et al. 2009a, 2013a, b; Kalinin et al. 2009, 2013; Yanilkin et al. 2009) toward the development of methods

for the synthesis of macrocycles with quinoxaline structures and demonstrate the possibility of designing macrocyclic systems based on a chelating compound, *m*-bis (3-phenylimidazo[1,5-*a*]quinoxalin-4(5*H*)-on-1-yl)benzene **164** (Mamedov et al. 2004a, 2007). The presence of carbamoyl groups in the quinoxalin-2(1*H*)-one fragments of compound **164** suggests that the coupling reaction involves nitrogen or oxygen atoms, with the formation of *N*,*N*′-, *N*,*O*-, and *O*,*O*′-alkylated products depending on the spacer type and length, and also influenced by the experimental conditions.

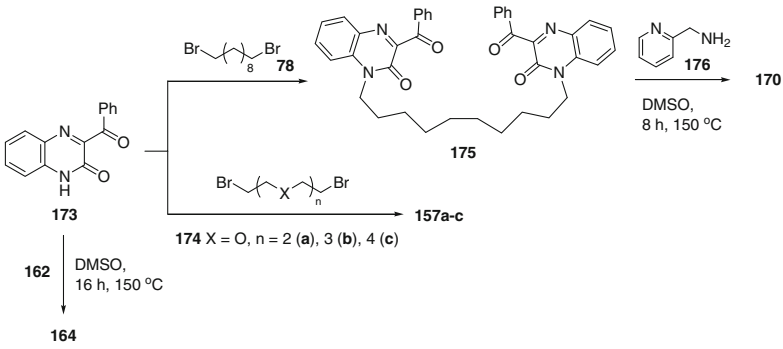
The reaction of *m*-bis(3-phenylimidazo[1,5-*a*]quinoxalin-4(5*H*)-on-1-yl)benzene **164** and the dibromide **167** (Moore et al. 1977) in the presence of potassium *tert*-butoxide in DMSO, or in the presence of K_2CO_3 in DMF gave the products **168** and **169a**, **b**, which consisted of hemispherand (Lein and Cram 1985; Ruettimann et al. 1992) and calixarene (Vicens and Bohmer 1991) structural fragments, resulting from *N*,*N*′-alkylation according to the schemes [1 + 1] and [2 + 2] (Scheme 5.40) (Mamedov et al. 2014).

The isomer ratio obtained in this process depended on the base used. Seven isomers with the combined yield of 86 % were detected by matrix-assisted laser desorption/ionization mass spectroscopy (MALDI), and the main product according to HPLC data, which was identified as the [1 + 1]-*N*,*N*′-alkylation product **168**, was isolated in 57 % yield. The yields of two other products, apparently formed as a result of *N*,*O*- and *O*,*O*′-alkylation according to the scheme [1 + 1], were 4 and 2 %, while the yields of four products formed by the scheme [2 + 2] were 2, 2, 8, and 3 %. Of all the possible products, only the structure of the isolated and characterized macrocycle **168**, as well as the structures of the *N*,*N*′-alkylation products formed according to the scheme [2 + 2] are presented in the scheme, because the products from *N*,*O*- and *O*,*O*′-alkylation of quinoxalines were unstable and difficult to isolate (Mamedov et al. 2009a), unlike the *N*,*N*′-alkylation products (Mamedov et al. 2013a; Kalinin et al. 2013). The product **168** was isolated by column chromatography, and its structure was established from spectral data, including a set of NMR experiments (^{1}H, ^{13}C, 2D) and X-ray structural analysis. Compounds **169a**, **b** were obtained in the form of a mixture that could not be separated into the individual isomers.

The pyridinyl substituent in position 1 of 1,10-bis-{3-phenyl-1-(pyridin-3-yl) imidazo[1,5-*a*]quinoxalin-4-on-5-yl}decane **170**, which then would be subjected to alkylation with alkyl dihalides with the formation of pyridinium salts, opens the



Scheme 5.41 Reaction of 1,10-bis(imidazoquinoxaline)decane with the α,α′-dibromo-*m*-xylene



Scheme 5.42 Synthesis of precursors for macrocycles with two imidazoquinoxaline moieties

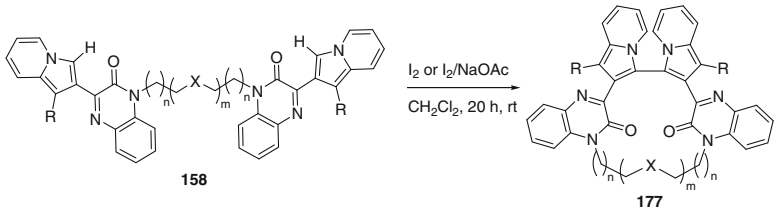
possibility of building imidazoquinoxaline macrocycles with two pyridinium salt fragments. The interaction of 1,10-bis(imidazoquinoxaline) decane **170** with the α,α′-dibromo-*m*-xylene **171** in acetonitrile solution at high dilution brings about the $1^3,7^3$-diphenyl-$1^4,7^4$-dioxa-1,7(1,5)-diimidazo[1,5-*a*]qunoxalina-2(3,1),6(1,3)-dipyridina-4(1,3)-benzenacycloheptadecaphane-$2^1,6,^1$-ylium dibromide **172** in a 60 % yield (Scheme 5.41). Unfortunately, the analytically pure sample of **172** when separated from the reaction mixture was only 25 % (Kalinin et al. 2013).

Compounds **164** and **170** with the two imidazoquinoxaline moieties have been prepared from the 3-benzoylquinoxalin-2-ones **173** with *m*-xylylenediamine **162** (Mamedov et al. 2004, 2007, 2009b), and from the reaction of 1,10-bis (3-benzoylquinoxalin-2-on-1-yl)decane **175** with β-picolylamine **176** (Kalinin et al. 2013) (Scheme 5.42). The precursors of macrocycles–1,*n*-bis(3-benzoylquinoxalin-2-one)alkanes **157a**–**c**, **175**–were prepared by the alkylation of 3-benzoylquinoxalin-2-one **173** (Mamedov et al. 1989, 2002a, b, 2003a, b, 2004b; Mamedov and Nuretdinov 1992; Gorbunova and Mamedov 2006) with the 1,*n*-dibromooxaalkanes **174a**–**c** and 1,10-dibromodecane **78** and on heating in dioxane with KOH (Mamedov et al. 2006).

5.4.3 Bis(3-indolizinylquinoxalin-2-on-1-yl)alkanes

1,*n*-Bis-[3(1-phenylindolizin-2-yl)quinoxalin-2-on-1-yl]oxaalkanes **158** with molecular iodine at room temperature in methylene chloride in dilution proceeds with intramolecular cyclization and the formation of the macrocycles **177** with redox-active biindolizine moieties (Table 5.3). Earlier the salts of Fe(III) in a stream of oxygen, Pt/C, 10 % Pt, Pd/C, $K_3Fe(CN)_6$ were used as reagents or as catalysts for the transformation indolizine to biindolizin. However, it was not always possible to obtain the biindolizine derivatives in good yields, especially when indolizine derivatives with hetaryl or withdrawing substituents were used (Andruzzi et al. 1988; Kreher et al. 1997; Sonnenshein et al. 1998). The application of molecular

Table 5.3 A facile iodine mediated synthesis of diquinoxalinadiindolizinacyclophanes



158 177

Entry	158	R	X	m	n	177	Yield, %[a], (%[b])
1	**158a**	Ph	*m*-C_6H_4	0	1	**177a**	30 (50)
2	**158b**	Ph	CH_2	2	2	**177b**	49 (59)
3	**158c**	Ph	O	1	1	**177c**	35 (60)
4	**158d**	Ph	O	2	1	**177d**	68 (74)
5	**158e**	Ph	O	3	1	**177e**	69 (92)
6	**158f**	Ph	O	3	5	**177f**	79 (86)
7	**158h**	Ph	O	4	1	**177h**	75 (86)
8	**158i**	Ph	*o*-$(OCH_2CH_2O)C_6H_4$	1	1	**177i**	58 (67)
9	**158j**	Ph	*m*-$(OCH_2CH_2O)C_6H_4$	1	1	**177j**	60 (69)
10	**158k**	Ph	O	5	3	**177k**	60 (80)
11	**158l**	Ph	O	5	5	**177l**	63
12	**158m**	H	O	3	1	**177m**	(50)

[a]Yields of isolated products when molecular iodine was used as oxidative reagent.
[b]Yields of isolated products when the binary system (I_2-NaOAc) has been used instead of molecular iodine.

iodine makes it possible to achieve good results not only in the oxidation of 3-(1-phenylindolizin-2-yl)quinoxalin-2-ones, but also in (with) podands with two terminated 3-(indolizin-2-yl)quinoxalin-2-one fragments (Mamedov et al. 2007, 2013a, b; Kalinin et al. 2009). Compounds with two indolizine fragments, **158c**, **e**, **h**, **m** successfully underwent intramolecular cyclization to form macrocycles **177c**, **e**, **h**, **m** in high yields when exposed to the I_2–NaOAc binary system (entries 3, 5, 7, 12). In addition, in the case of molecular iodine the macrocyclization of podands **158d**, **e**, **l** gave products **177d**, **e**, **l** in high yields (entries 4, 5, 11). The use of molecular iodine for the oxidation of podand **158c** gave the macrocycle **177c** (of a smaller size) in a moderate yield. In this case, there appeared to be products of oligomerization in the mixture and a significant amount of the starting substrate

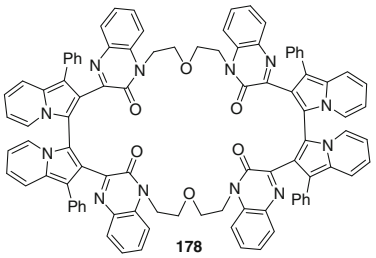


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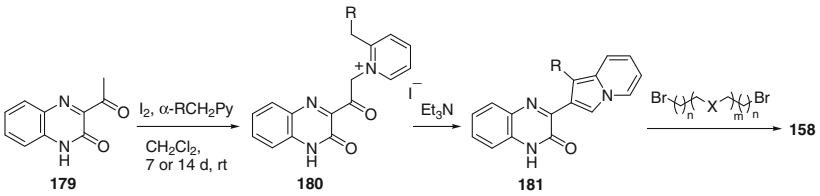
Fig. 5.11 Macrocycle–product of the dimerization of 1,5-bis[3-(1-phenylindolizin-2-yl) quinoxalin-2-on-1-yl]-3-oxapentane

158c remained. The application of the binary system (I_2–NaOAc) increased the yield of the macrocycle **177c** up to 60 % and the macrocyclic dimer **178** was obtained in a 24 % yield (entry 3, Fig. 5.11). When decreasing the excess of molecular iodine from 2.3-fold to 2-fold in the case of a podand **158m**, it was possible to synthesize macrocycle **177m** with the free 1,1′-CH groups via the regioselective oxidative coupling of the 3,3′-CH groups of the 2,2′-biindolizine system (entry 12) (Mamedov et al. 2013a).

Macrocycles **177k**, **l** with the hexaethylene glycol spacers and their precursors **158k**, **l** exist as hydrates (Kalinin et al. 2009).

Heterocyclophane **177e** was also obtained on a platinum cylindrical electrode by the preparative electrochemical oxidation of podand **158e** in a diaphragm (cellulose) glass electrolyzer. The electrosynthesis was carried out for 4 h. The mass spectrometric investigations of the mixture after the electrolysis showed the existence of two macrocyclic products: **152e** (m/z = 830), and the macrocyclic dimer (m/z = 1660). The preparative yield was 40 % (Mamedov et al. 2007). There was no starting compound in the solution.

The synthesis of the precursors of macrocycles **177** is based on 3-acetylquinoxalin-2-one **179** (Mamedov et al. 2005a) and involves the following three stages: (a) the interaction of **179** with α-phenylpicoline and molecular iodine (the Ortoleva-King reaction), (b) the intramolecular condensation of the picolinium salts **180** in the presence of triethylamine (the Chichibabin reaction) (Mamedov et al. 2005b), (c) the alkylation of 3-(1-phenylindolizin-2-yl)quinoxalin-2(1*H*)-ones **181** by dibromoalkanes on the nitrogen atoms of an amide group (Kalinin et al. 2009; Mamedov et al. 2013b) (Scheme 5.43).



Scheme 5.43 The sequence for the synthesizing podands with two terminal 3-(1-phenylindolizin-2-yl)quinoxalin-2(1*H*)-one moieties from 3-acetylquinoxalin-2-one

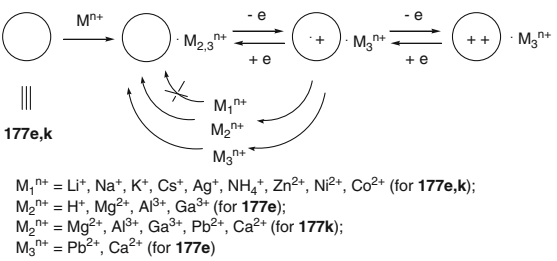


Fig. 5.12 Binding by macrocycles **177** of ions of metals

The binding of a wide range of metal cations by macrocycles **177e** and **177k** was investigated with cyclic voltammetry. All the ions can be divided into three groups. The ions of the first group (Li^+, Na^+, K^+, NH_4^+) did not affect the characteristics of the oxidation peak, and, apparently, were not linked with the macrocycle. The ions of the second group (Mg^{2+}, Al^{3+}, Ga^{3+}) shifted the first peak of oxidation and the peak of heterocyclophane **177** toward positive potentials. These effects increase with the increasing metal ion concentration. The second and the third oxidation peaks are not changed with the introduction of the metal ion. At a certain concentration of the metal ion, the potential of the first peak equals the potential of the second peak and as a result instead of two peaks only one two-electronic peak of oxidation is fixed on the CVA curve. Therefore, for the second group of ions, redox-switchable binding by a macrocycle **177e** is observed: the parent compound binds ions and the cation radical and dications do not bind. When introducing ions of the third group (Ca^{2+}, Pb^{2+}) as well as ions Ba^{2+}, the first two peaks of oxidation of a macrocycle **177e** do not change the parameters, but the second peak becomes reversible (Fig. 5.12). These ions are bound not only to the parent but also to the cation radical and the dication of **177e**. Such a binding of ions Ca^{2+}, Pb^{2+}, and Ba^{2+} leads to an unusual stability of dication **177e**. Interestingly, on increasing the concentration of the metal ion the third peak substantially disappears. This is quite natural as the stabilization of the dication prevents the formation of the product which is oxidized at potentials of the third peak (Yanilkin et al. 2007, 2009, 2010, 2011).

5.5 Both Resorcin[4]arenes and Quinoxalines in the Synthesis of Macrocycles

The versatility of resorcinarene-derived cavitands has generated a wealth of host molecules (Rebek 1999; Jasat and Sherman 1999; Hof et al. 2002; Rudkevich 2002; Laughrey et al. 2003; Shivanyuk et al. 2002; Barrett et al. 2002; Paek et al. 2003; Pirondini et al. 2003). Tetraquinoxaline-spanned resorcinarene cavitands **182** were introduced by Cram in the early 1980s (1983) and have been used extensively to study host–guest interactions (Moran et al. 1982; Dalcanale et al. 1989; Moran et al. 1991; Soncini et al. 1992; Careri et al. 1997; Bianchi et al. 2003). Of particular interest is therin to undergo a reversible thermal switch from the vase to the kite conformation (Fig. 5.13). The vase exists at temperatures of 45 C and above, while the kite exists exclusively below −60 °C.

The interaction of resorcin[4]arenes with the 2,3-dichloroquinoxaline proceeding with the formation of tetraquinoxaline-spanned cavitands has been investigated under various conditions (Scheme 5.44). Thus, tetramethylcalixresorcin[4]arene **8** (A = H, R = Me) with four equivalents of 2,3-dichloroquinoxaline **183** (B = H) in DMF in the presence of KOH leads to the teraquinoxaline-spanned cavitands **182b** in the 34 % yield (Moran et al. 1982). The authors did not manage to exempt the cavitand **182b** from the 10 molecules of DMF. In DMF with KOH or K_2CO_3, they lead to the **182a–e**, **k** in 30–44 % yields (Moran et al. 1991; Bianchi et al. 2003).

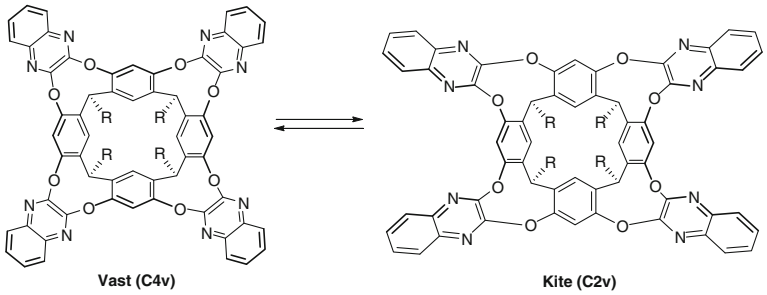
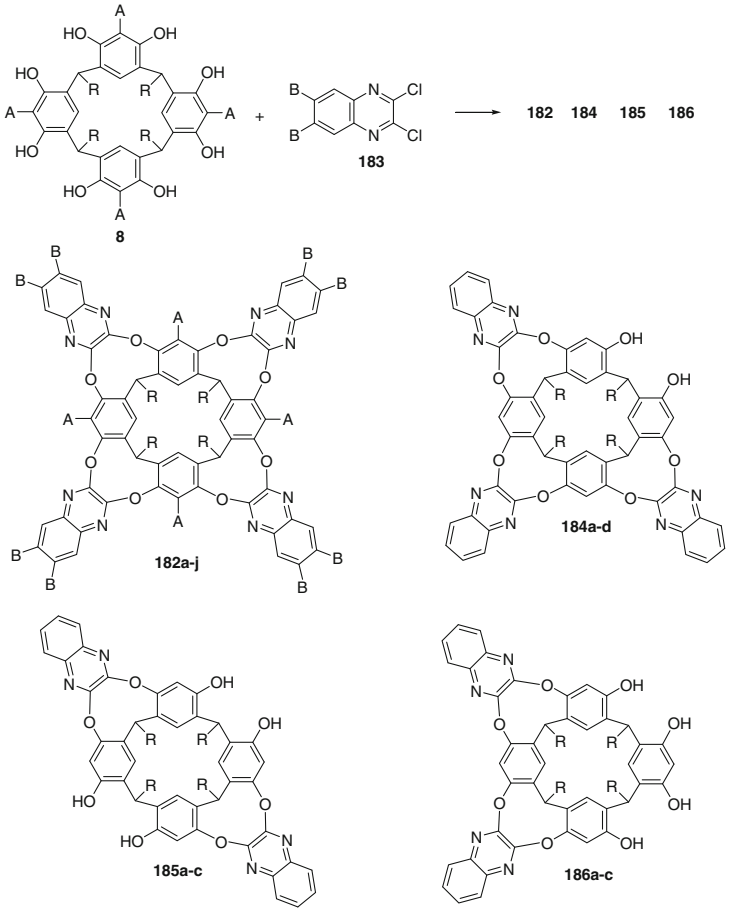


Fig. 5.13 Structural representation for the tetraquinoxaline-bridged cavitand **182**, illustrating the vase (S4v)–kite (C2v) equilibrium

The replacement of DMF by DMSO, and KOH or K_2CO_3 by Cs_2CO_3 leads to an essential increase in the yield of a cavitand. Under these conditions, **182b**, **f**, **g** have been obtained in 83, 77, and 68 % yields, respectively (Moran et al. 1991). The use of a $CsHCO_3$ as a base leads to the cavitand **182b** in a 30 % yield along with the cavitand **184d** in a 40 % yield (Moran et al. 1991).

The reduction of excess of 2,3-dichloroquinoxaline allows formation of cavitands with a smaller number of systems. Thus in the presence of KOH, the interaction of the tetramhexylcalixresorcin[4]arene **8** (A = H, R = *n*-C_6H_{13}) with four equivalents of 2,3-dichloroquinoxaline **183** (B = H) in DMSO leads to the teraquinoxaline-spanned cavitands **182h** in a 88 % yield (Dalcanale et al. 1989; Rudkevich et al. 1998), whereas with three equivalents of 2,3-dichloroquinoxaline **183** (B = H) there occurs the formation of the threequinoxaline-spanned cavitands **184c** (R = *n*-C_6H_{13}) in 53 % yield and the teraquinoxaline-spanned cavitands **182h** in 27 % yield (Soncini et al. 1992). As a result of the interaction of tetramhexylcalixresorcin[4]arene **8** (A = H, R = *n*-C_6H_{13}) with two equivalents of 2,3-dichloroquinoxaline **8** (B = H), a mixture of cavitands with two or three quinoxaline fragments **184c**–**186c** with 20, 4 and 20 % yields, respectively (Azov et al. 2006) is formed. The predecessors of cavitands, i.e, calixresorcin[4]arenes are obtained under the Zinke–Ziegler reaction (Zinke and Ziegler 1941) condition by the condensations of the four moles of resorcinol with the corresponding aldehyde or methylresorcinol. The introduction of four bromine atoms into the cavitand skeleton was performed by usual bromination. The yields of calixresorcin[4]arenes were 60–95 % (Moran et al. 1982, 1991).

All quinoxaline-containing cavitands are unstable to phenoxide nucleophiles (Castro et al. 2004). This has provided the opportunity to explore the deliberate excision of one and then two quinoxaline units from the easily available tetraquinoxaline cavitand (Moran et al. 1982; Dalcanale et al. 1989; Moran et al. 1991; Castro et al. 2004) with an appropriate nucleophile. Catechol offers two appropriately spaced oxygen atoms to efficiently attack the quinoxaline moiety, and the quinoxaline-catechol adduct formed thereby is a known, stable compound and a convenient TLC marker of the reaction progress (Smith et al. 1992).

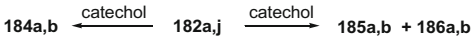


184-186 R = *n*-C_5H_{11} (**a**), *i*-C_4H_9 (**b**), *n*-C_6H_{13} (**c**), Me (**d**)
182 R = *n*-C_5H_{11}, A = B = H (**a**); R = Me, A = B = H (**b**); R = $(CH_2)_5Cl$, A = B = H (**c**);
R = $(CH_2)_4Me$, A = H, B = Me (**d**); R = $(CH_2)_5Cl$, A = Me, B = H (**e**);
R = A = Me, B = H (**f**); R = A = B = Me (**g**); R = *n*-C_6H_{13}, A = B = H (**h**);
R = *n*-C_6H_{13}, A = B = H (**i**); R = *i*-C_4H_9, A = B = H (**j**); R = $(CH_2)_8CH{=}CH_2$, A = B = H (**k**)

Scheme 5.44 Synthesis of calixresorcin[4]arenes with two-, three-, and four- quinoxaline moieties

Table 5.4 summarizes the results for the preparation of cavitands **182a**, **j**, **184a**, **b**–**186a**, **b**. Entries 1–3 provide results for the triquinoxaline-spanned cavitand **184a**, **b**, while entries 4–8 refer to the preparation of diquinoxaline-spanned cavitands **185a**, **b** and **186a**, **b**. Various bases were compared, with the inclusion of the CsF based on related successful results with this base. In all cases, catechol was added to a heated mixture of tetraquinoxaline-spanned cavitand and base in the DMF solvent. The solubility of the tetraquinoxaline-spanned cavitand was improved at higher temperatures, and the reaction times were appreciably shortened. Employment of DMF resulted in slightly cleaner mixtures than those of

Table 5.4 Reaction conditions and yields (%) of cavitands **182a**, **j**, **184a**, **b–186a**, **b**



Entry	Base (equiv)	Catechol equiv (*t*)	**182** (Yield)	**184** (Yield, %)	**185** (Yield, %)	**186** (Yield, %)
1	CsF (5)	1.1 (30 min)	10	63	9	trace
2	CsF (20)	1.1 (30 min)	6	71	trace	trace
3	K_2CO_3 (20)	1.3 (1.2 h)	0	60	12	trace
4	CsF (20)	2.3 (35 min)	0	13	35	7
5	CsF (20)	3.2 (40 min)	0	3	60	11
6	Cs_2CO_3 (20)	3.2 (1 h)	0	2	53	10
7	K_2CO_3 (20)	3.3 (1 h)	0	21	43	3
8	KF (20)	3.3 (24 h)	trace	9	38	4

DMSO (Castro et al. 2004). All the reactions were sensitive to the amount of the catechol used and less so to the amount of base. Successful reactions were completed in less than 1 h.

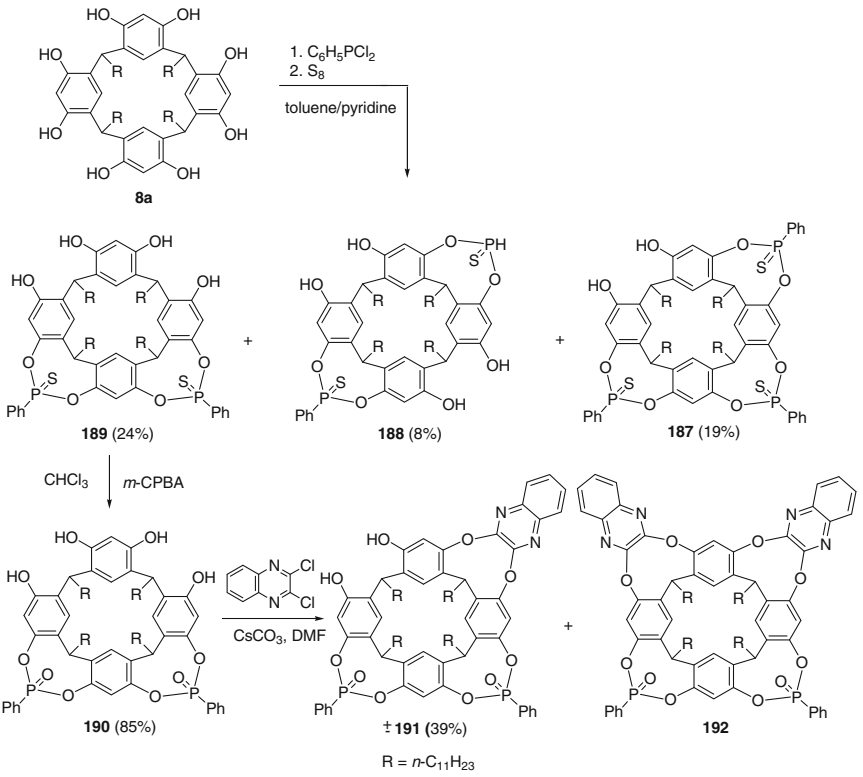
An inherently chiral AB*ii* diphosphonatocavitand (±)-**191** bearing a single quinoxaline bridging moiety was synthesized on the basis of resorcin[4]arene **8a** (R = *n*-$C_{11}H_{23}$) according to the following scheme which involves five-stage processes (Vachon et al. 2010) (Scheme 5.45).

(1) The acid-catalyzed co-condensation between resorcinol and dodecanal (Timmerman et al. 1996), predominantly led to resorcin[4]arene **8a** (Weinelt and Schneider 1991).

(2) The treatment of **8a** with two equivalents of dichlorophenylphosphine (Dubessy et al. 2009) in the presence of pyridine was followed by the addition of sulfur in situ (Bibal et al. 2002). This gave rise to three major compounds: the trithiophosphonate *iii*PS derivative **187** (19 %) and the two dithiophosphonatocavitands AC*ii*PS **188** (8 %) and AB*ii*PS **189** (24 %), which were separated by column chromatography. Despite the fact that this method has already been reported (Cantadori et al. 2008), the isolation of compounds of type AB*ii*PS is unprecedented.

(3) The partially bridged compounds, with the inward orientation of the P = O groups, were obtained by following the two-step synthesis previously described for the synthesis of triphosphonatocavitands (Dubessy et al. 2009). Contrary to the compounds of type *iii* **187** or AC*ii* **188**, the AB*ii* **189** structure can be desymmetrized by adding a third and different bridge onto the crown of the cavitand.

(4) The transformation of the AB*ii*PS **189** into AB*ii*PO **190** using a slight excess of *m*-CPBA (3 equiv) as an oxidant was performed and occurred with retention of configuration, and the P = O groups adopted the inward orientation (Herriott 1971). After chromatography, the phosphonatocavitand **190** was isolated in a 89 % yield.



Scheme 5.45 Synthesis of diphosphonatocavitands

(5) The synthesis of quinoxaline bridges cavitand. The synthesis of quinoxaline bridges has been used for the preparation of deep cavity cavitands (Cram 1983). Here, the addition of 1 equiv of 2,3-dichloroquinoxaline mainly leads to (±)-**191** bearing one quinoxaline bridge, and to the bis-quinoxaline **192**, isolated by column chromatography.

Thus an inherently chiral AB*ii* diphosphonatocavitand (±)-**191** bearing a single quinoxaline bridging moiety was synthesized and resolved by the chiral HPLC.

In 2008, Francois Diederich and co-workers reported the syntheses and extensive binding, molecular dynamics, and switching studies of the switchable baskets **194** (Fig. 5.14) (Gottschalk et al. 2008). Resorcin[4]arene-based container molecules accommodate suitable guests within well-defined cavities and completely surround them (Gottschalk et al. 2008). The molecules show a remarkable binding selectivity as a consequence of their precisely defined geometry. Portals delimiting the cavity are opened upon the addition of acid and then binding is suspended as a

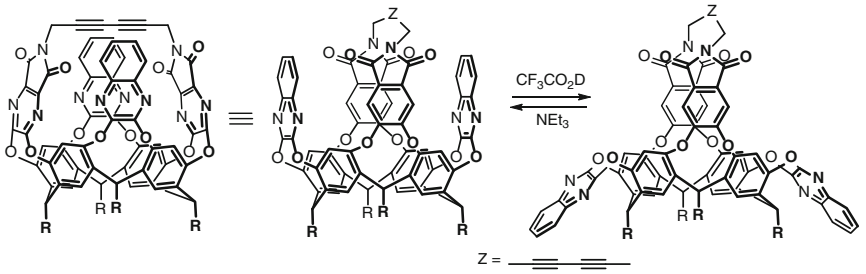
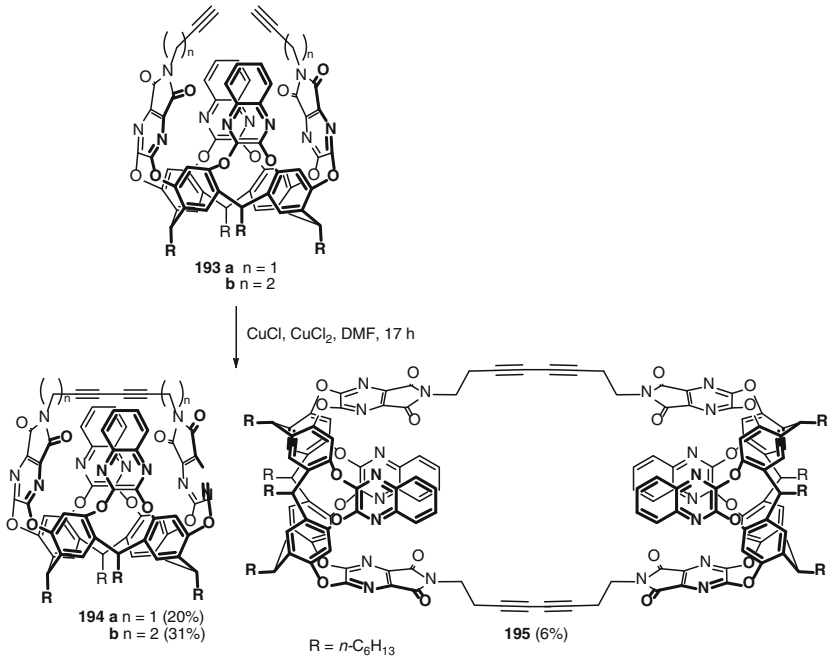


Fig. 5.14 The closed and open conformations of **194a**. The equilibria can be controlled by adjusting $[H^+]$ in their solutions



Scheme 5.46 Synthesis of switchable baskets and tube from open-top precursor cavitands

result of the induced change in structure. The process is fully reversible; the neutralization of the solution completely recovers the initial state (Gottschalk et al. 2007).

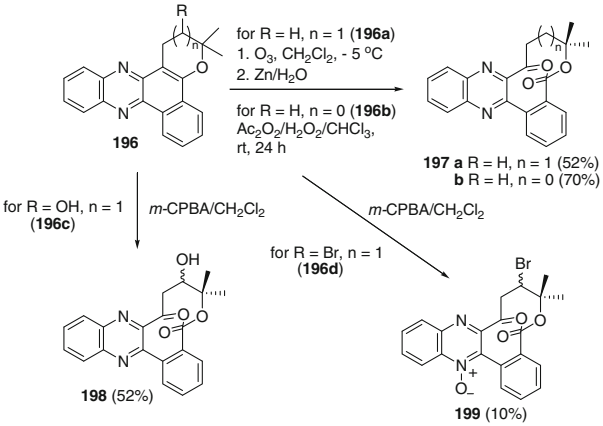
The key step in the synthesis of **194** is an oxidative acetylenic coupling reaction of open-top precursor cavitands **193**. Intramolecular coupling of **193b** affords the basket **194b** along with a dimeric structure and the switchable tube **195**, in a ratio of 2/6 ≈ 10:1 (Scheme 5.46). The two products can be separated by preparative high performance gel-permeation chromatography (GPC) (Gottschalk et al. 2007).

5.6 Other Methods of Synthesis

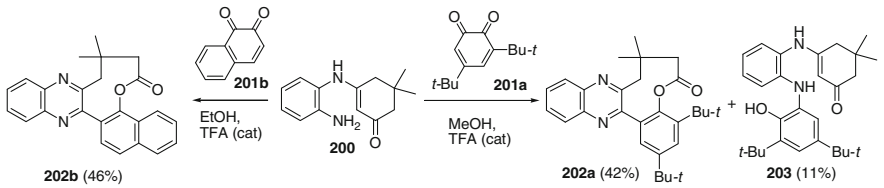
In addition to the above three groups of methods of constructing quinoxaline macrocycles, there are other methods that are neither based on any quinoxaline derivatives nor on podand quinoxaline terminal fragments or macrocycles.

5.6.1 Pyran 1,4-Diazaphenanthrenes

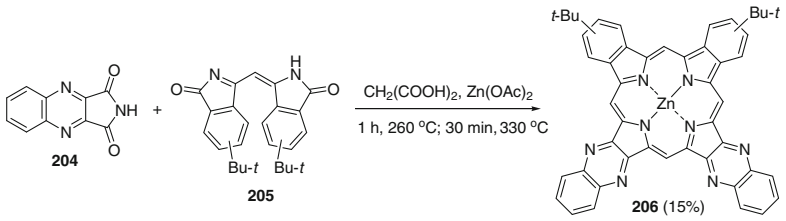
The benzophenazines **196** behave similarly as 1,2,9,10,11,12-hexahydrobenzo[*a*]-furo[2,3-*c*]phenazines **535** (see Sect. 2.6.2.11) (Pérez-Sacau et al. 2005), in terms of their oxidation by ozone and *m*-chloroperbenzoic acid (Silva et al. 2005) provide the corresponding macrocycles **197–199**. However, in the case of **196d**, a complex



Scheme 5.47 Synthesi of 9- and 10-membered macrolactones with quinoxaline moiety



Scheme 5.48 Synthesis of macrolactones



Scheme 5.49 Synthesis of unsymmetrical porphrines containing containing *tert*-butylbenzo and quinoxaline fragments

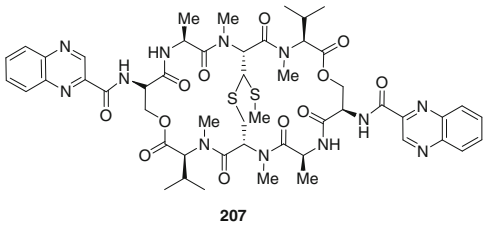


Fig. 5.15 Structure of macrocycle *Ehinomicin*

mixture of products was obtained, from which it was possible to isolate **199**, as the corresponding *N*-oxide bromomacrolide, in a low (10 %) yield (Scheme 5.47).

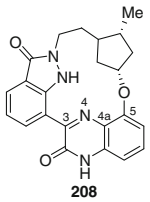
These macrolactones from benzo[*a*]phenazine were evaluated for their antimycobacterial potential and **197b** appeared to have an MIC of 0.62 mg per mL on *Mycocabterium tuberculosis* H37Rv (Silva et al. 2009).

3-(2-Aminophenylamino)-5,5-dimethyl-2-cyclohexen-1-one **200** with 3,5-di-*tert*-butyl-1,2-benzoquinone **201a** and an acidic catalyst led to a mixture of 8,8-dimethyl-7,8,9-trihydro-2,4-di-*tert*-butylbenzo[2,3]oxonino[4,5-*b*]quinoxalin-6-one **202a** and 3-[2-(2-hydroxy-3,5-di-*tert*-butylphenylamino)]-5,5-dimethyl-2-cyclohexen-1-one **203** (Scheme 5.48) (Ukhin et al. 2012). The reaction proceeds rapidly with CF_3CO_2H as catalyst and under short heating, but does not occur at all in the absence of catalyst. The reaction also proceeds in CH_3CO_2H but the most appropriate solvents proved to be alcohols (MeOH, EtOH). The products **202a** and **203** are generated as a result of quinone attachment to different centers of **200**. Under similar conditions an analogoues compound, macrolactone **202b,** was isolated from **200** and 1,2-naphthoquinone **201b**.

5.6.2 *Quinoxaline-2,3-dicarboximide*

The original method of synthesis of [*cis*-di(4-*tert*-butylbenzo)diquinoxalinoporphyrinato]zinc(II) **206** involves the reaction of 5-*tert*-butyl-3-(5-*tert*-butyl-3-oxo-2,3-didihydro-1*H*-isoindol-1-ylidenemethyl)-1*H*-isoindol-1-one **205** with the excess quinoxaline-2,3-dicarboximide **204** and malonic acid in the

Fig. 5.16 Structure of macrocycle of second type



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presence of zinc(II) acetate (Galanin and Shaposhnikov 2007) (Scheme 5.49). In this case, imide **204** has been prepared by passing dry NH_3 through molten quinoxaline-2,3-dicarboxylic acid at 250 °C over 10 min.

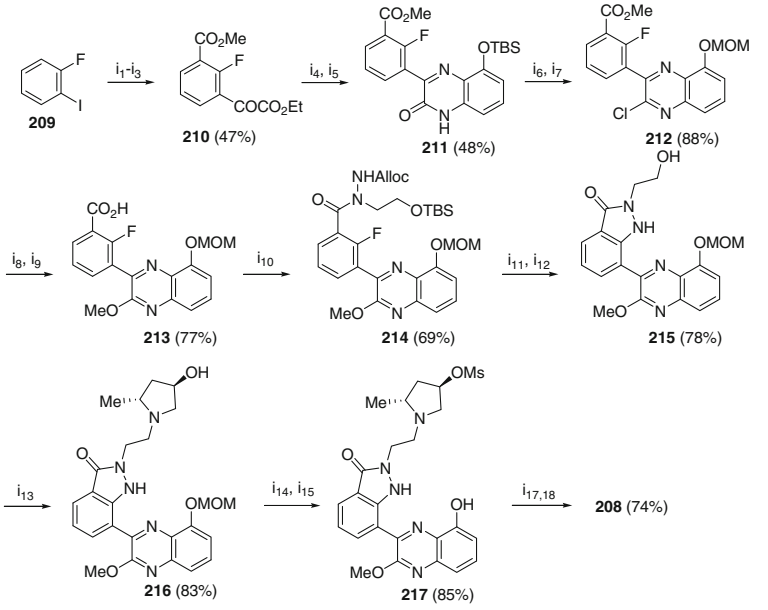
5.6.3 *Macrocyclic Quinoxaline Compounds as Anticancer Drugs and Inhibitors of Hepatitis C Virus*

There are three types of the quinoxaline macrocyclic compounds known with important pharmacological properties. They differ in whether the quinoxaline fragment enters the structure of the macrocyclic system and if it does, then what follows.

The first type is the macrocycle *Ehinomicin* **207** (Fig. 5.15), which is in the Negver handbook "Organic Chemical Drugs and their Synonyms," with over fifty other pharmacologically interesting compounds, i.e, derivatives of quinoxaline (Negwer and Scharnow 2001; Mamedov and Zhukova 2012, 2013). Compound **207** is an antibiotic applied as an antineoplastic preparation in the chemotherapy of cancer, a synonym of the medicines NSC-526417, *Quinomycin A*. In **207**, the quinoxaline fragments are not acting as structure-forming parts of the macrocycle, and are part of the amide bonds, which are formed between the amino groups of a macrocycle and the carboxyl groups of the quinoxalin-2-carbonic acids.

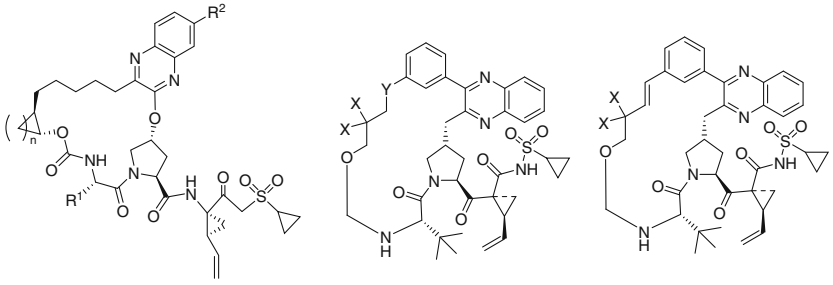
In the **second type** of macrocycles, i.e., **208** (Fig. 5.16), the design the quinoxaline system represents the four-atomic fragment C(3)–N(4)–C(4a)–C(5) (Kawanishi et al. 2006).

The design of a novel series of cyclin-dependent kinase (CDK) inhibitors with a macrocyclic quinoxaline-2-one **208** is reported (Kawanishi et al. 2006), where **208** was synthesized as shown in Scheme 5.50. The deprotonation of the fluorine-adjacent position of 1-fluoro-2-iodobenzene **209**, with LDA, followed by the carbon dioxide trapping and then esterification of the carboxylic acid, led to methyl 2-fluoro-3-iodobenzoate. The iodomagnesium exchange of methyl 2-fluoro-3-iodobenzoate according to Knochel's procedure (Knochel et al. 2003) followed by chloroglyoxylic acid ethyl ester resulted in ketoester **210**, which was coupled with 3-[(*tert*-butyldimethylsilyl)oxy]benzene-1,2-diamine to quinoxaline-2-one, **211**. The activation of the 2-position of quinoxaline-2-one **211** via the corresponding 2-chloroquinoxaline with $SOCl_2$ was followed by the



i_1 = LDA, CO_2, THF; i_2 = H_2SO_4 conc, MeOH; i_3 = *i*-PrMgCl; i_4 = ClCOCOEt;
i_5 = 3-[(*tert*-butyldimethylsilyl)oxy]benzene-1,2-diamine;
i_6 = $SOCl_2$, DMF; i_7 = MOMCl, TBAF, THF; i_8 = NaH, MeOH; i_9 = NaOH, THF, MeOH, H_2O;
i_{10} = [*t*-Bu(Me)$_2$SiOCH$_2$CH$_2$]$_2$NNHCO$_2$All, DMC, Et_3N, $CHCl_3$; i_{11}= Pd(PPh)$_4$, HCO_2H, Et_2NH, THF;
i_{12} = *i*-Pr_2NEt, DMF; i_{13} = MsCl, *i*-Pr_2NEt, $CHCl_3$; i_{14} = (3R,5R)-5-methylpyrrolidin-3-ol;
i_{15} = MsCl, *i*-Pr_2NEt, $CHCl_3$; i_{16} = TFA/H_2O; i_{17} = K_2CO_3/DMF; i_{18} = TFA/H_2O

Scheme 5.50 The sequence of the reactions for synthesizing cyclin-dependent kinase (CDK) inhibitors with a macrocyclic quinoxaline-2-one

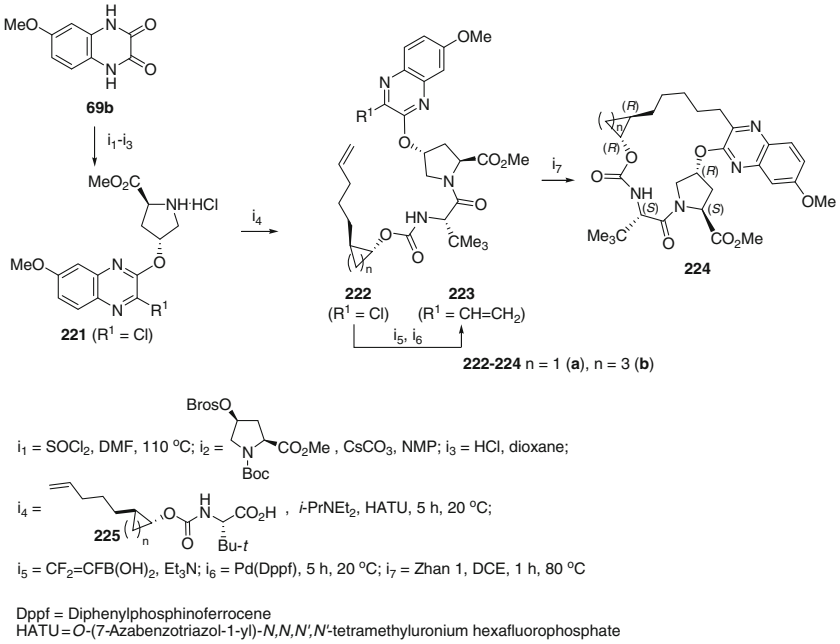


218 a n = 1, R^1 = *t*-Bu, R^2 = OMe
b n = 3, R^1 = *t*-Bu, R^2 = OMe
c n = 3, R^1 = *c*-Pentyl, R^2 = H

219 a Y = CH_2, X = H
b Y = O, X = Me

220 a X = H
b X = F

Fig. 5.17 Structures of the synthesis of the **third type** of macrocycles



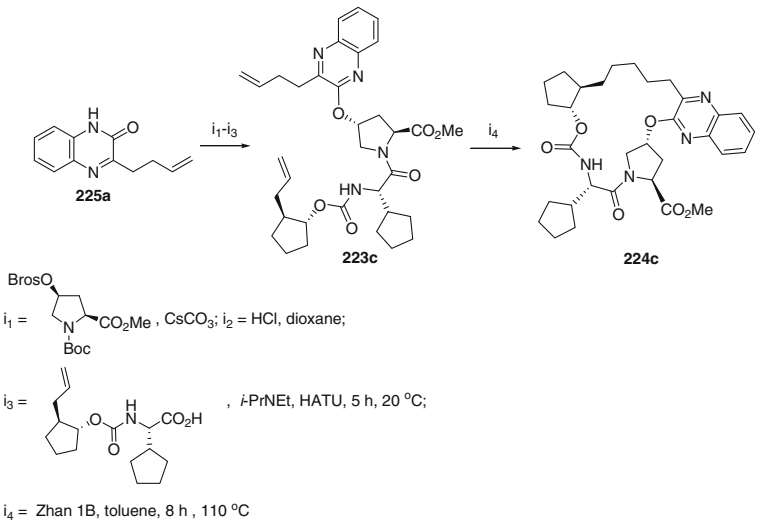
Scheme 5.51 The sequence of the reactions for synthesizing macrocycles **224a**, **b,** i.e., the precursores of of the third type of macrocycles **218a**, **b**

replacement of the TBS group by a MOM group with TBAF to yield **212**. The addition of sodium methoxide at the 2-position of 2-chloroquinoxaline followed by hydrolysis with NaOH gave compound **213**. Allyl 2-[2-(*tert*-butyldimethylsilyloxy) ethyl]hydrazinecarboxylate (Hirai et al. 2004, 2005) was condensed with **213** to yield **214**. Under basic conditions, the deprotection of the Alloc group of compound **214** in the presence of a palladium catalyst followed by cyclization to indazol-3-one gave compound **215**. The alcohol of **215** was mesylated and then aminated with (3*R*,5*R*)-5-methylpyrrolidin-3-ol to yield **216**. The mesylation of **216** followed by the deprotection of the MOM group with TFA at room temperature led to **217**. Under basic conditions, the macrocyclization of **217** followed by the deprotection of the methyl group with TFA under reflux afforded **208**.

The macrocycle **208** is the inhibitor of the cylin-dependent kinase (Cdks) (Hirai et al. 2011).

For the synthesis of the **third type** of macrocycles, i.e., **218**–**220,** the quinoxaline system gives off a two-atomic fragment C(2)–C(3) (Liverton et al. 2008; Gai et al. 2009; Harper et al. 2010, 2012) (Fig. 5.17).

The procedure for the synthesis of macrocycles **224a**, **b,** i.e., the precursores of **218a**, **b** is given in Scheme 5.51. The synthesis is based on the 3-chloroquinoxalin-2-ones. In this process, a 7-methoxy derivative has been obtained from 7-methoxyquinoxalin-2,3-dione **69b** by the treatment with thionyl chloride in DMF. 3-Chloroquinoxaline-2-ones are transformed into quinoxaline



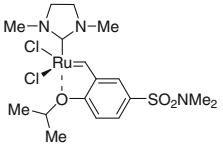
Scheme 5.52 The sequence of the reactions for synthesizing macrocycles **224c,** i.e., the precursores of of the third type of macrocycles **218c**

hydrochloride **221** with the pyrrolidine moiety in two stages. The acylation of the latter with **225** leads to **222a**, **b** which with trifluoro(vinyl)borate under basic conditions results in 3-vinylquinoxaline derivatives **223a**, **b**. The metathesis of **223a**, **b** in the presence of the Zhan 1[3] catalyst proceeds with the formation of macrocycles **224a**, **b** (Liverton et al. 2008; Harper et al. 2010, 2012). The two step processes **222a** → **224a** proceed in a 25 % overall yield.

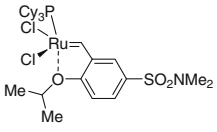
The initial stages of the preparation of the macrocycle **224c,** i.e., the precursor of **218c** proceed in a different way. Quinoxaline **225a** with a butylene substitute has been obtained by condensation of 4-methoxy-1,2-DAB with ethyl 2-oxo-hex-5-enoate. The subsequent four stages (i_1–i_4) of the processes proceed similarly to the stages (i_2–i_4, i_7) as in the synthesis of compounds **218a**, **b** (Scheme 5.52).

The synthesis of the precursors of **232**, **233,** i.e., the macrocycles **219**, **220** is based on the 3-(3-bromophenyl)quinoxalin-2-one **225b**. At the first stage, the methoxycarbonylpyrrolidine moiety was introduced through an oxygen atom of the carbamoyl group to form **226** (Scheme 5.53). Further, during the interaction of

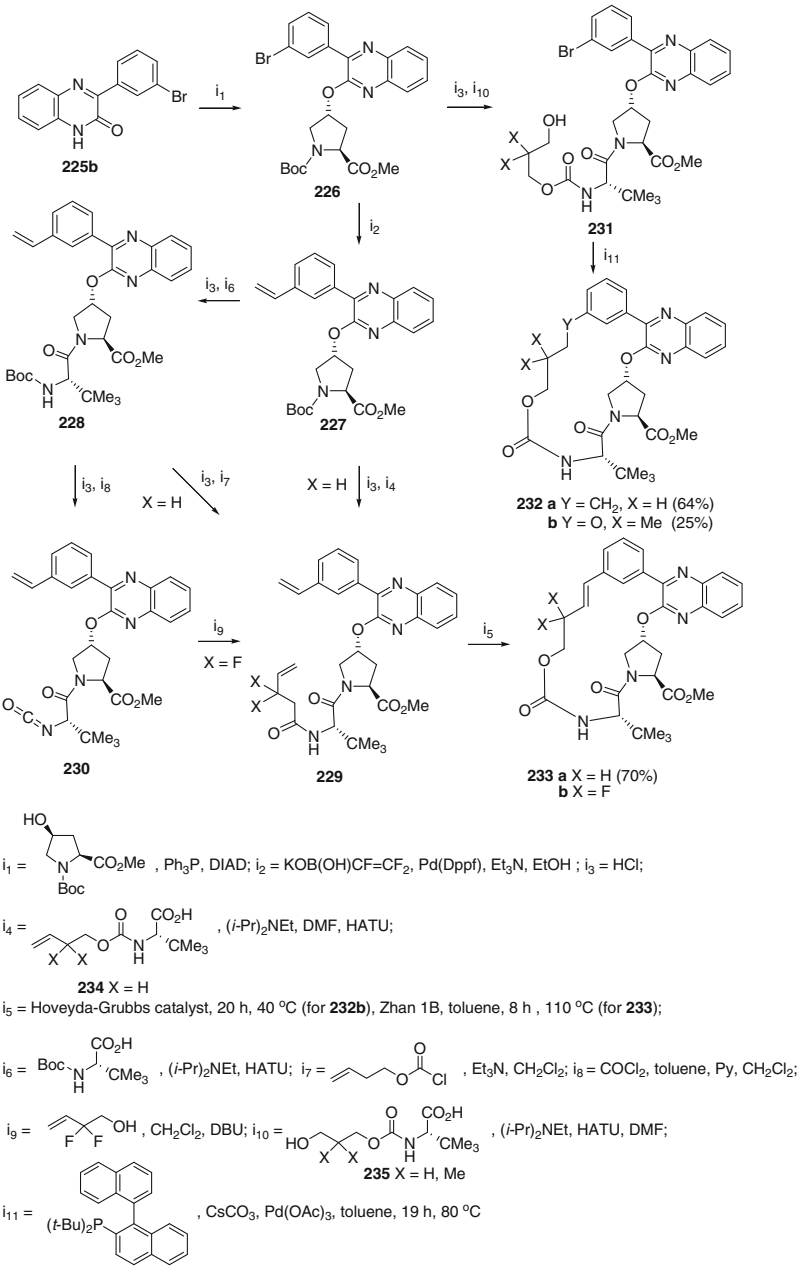
[3]The Zhan 1 catalysts are the commercially available ruthenium catalyst for **RCM** processes.



Zhan Catalist-1B



Zhan Catalist-1C



Scheme 5.53 The illustration the methods by which compounds of the invention may be prepared

potassium trifuloroborate the bromine atom was substituted by a vinyl fragment in **226**. The precursor for the cyclophane **229** was prepared from **227** either in one or in two (for X = H) or three stages (for X = F). As the result of metathesis, the formation of the macrocyclic **233** proceeds in the presence of ruthenium catalysts to form cyclophanes **233a**, **b** in good yields. In the synthesis of the macrocycle **232b** with the phenoxy moiety, the hydroxyamide fragment is incorporated into **226** in two stages; the removal of the protection group and the subsequent reaction with **230** forms a precursor of macrocycle, i.e., the compound **231**. The formation of the macrocyclic **232b** proceeds in the presence of a palladium catalyst under the influence of $CsCO_3$. However, in this case the yield is only 24 % (Gai et al. 2009).

Compounds **224**, **232**, **233** are transformed into water-soluble derivatives **218-220** possessing antiviral properties, as inhibitors of HCV.

5.7 Conclusion

There are a number of methods for the synthesis of quinoxaline macrocycles that have been successfully implemented for constructing quinoxalinoporphyrins, quinoxalinoporphyrazines, quinoxalinocrown ethers, quinoxalinocavitands, quinoxalinohemispherands, and "hybrid" macrocycles. In these macrocyclic systems, quinoxaline moiety(ies) were attached to the macrocyclic skeleton by the atoms N(1) and C(3), N(1) and N(4), C(2) and C(3), C(2) and C(8), C(6) and C(7). In these cases, macrocyclic systems in which the quinoxaline moiety is fixed in a macrocyclic skeleton by atoms of C(2) and C(3) are represented best of all. Considerably less attention is paid to their 6, 7 analogs, and all the others are represented in single works.

There have been obtained macrocycles the framework of which also includes other heterocyclic systems, e.g., pyrrole, pyridine, imidazole, ferrocene, indolizine, triazolothiadiazole, and benzopyrazole except the quinoxaline moiety. As a rule, a constantly growing interest is attached to the mutual influence of the heterocyclic fragments closely located toward each other. This is due to interest in the ample opportunities they hold for their practical application. Thus, the quinoxaline macrocycles with imidazole, pyrrole or ferrocene moieties are sensors for some anions and cations for the heavy metals. The combination in one molecule of macrocycles of quinoxaline, pyrrolidine, and benzopyrazolne fragments leads to the selective inhibition of the kinase, and the presence of pyrrolidine and amide fragments leads to an anti-hepatitis effect. Mono-, bis-, and tris- quinoxalinoporphyrins the macrocyclic skeleton of which included pyrrolequinoxaline and pyrrole moieties are attractive for the development of optical devices and materials.

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Chapter 6
Rearrangements of Quinoxalin(on)es for the Synthesis of Benzimidazol(on)es

6.1 Introduction

Benzimidazole derivatives have provided a large number of biologically active compounds that have been intensively used in medicinal chemistry as drugs (Elzahabi 2011). They are structural isosteres of naturally occurring nucleotides, which allow them to easily interact with the biopolymers of the living systems and different kinds of biological activity have been obtained. Some 2-aminobenzimidazoles displayed an appreciable antimicrobial effect. Their corresponding carbamate derivatives have been synthesized for their significant antifilarial activity in vivo (Sener et al. 1997). As to the high affinity that they display towards a variety of enzymes and protein receptors, they could be considered as pivotal structures in drug design (Sharma et al. 2006). The optimization of benzimidazole-based structures has resulted in marketed drugs, e.g., Omeprazole (Lindberg et al. 1986) and Pimobendan (Mannhold 1985) that are used as therapeutic agents in the treatment of peptic ulcer and congestive heart failure respectively. Many derivatives of benzimidazoles are well known for their antimicrobial (Nakamura 1955; Meral et al. 1997; Nofal et al. 2002; Zeynep et al. 2006; Singh et al. 2012), anthelmintic (Cuckler and Mezey 1966), antiviral (Hollinshead and Smith 1958; O'Sullivan and Wallis 1972; Zou et al. 1996; Simone et al. 2009), and antifungal (Kilgor and White 1970; Maxwell and Brody 1971; Walker et al. 1978; Elnima et al. 1981; Goin and Mayer 1995) activities. The antifungal agent Benomyl was first reported as a fungicide against a wide range of agricultural fungal diseases (Tomlin 1994). Many years later, it proved to be a potent antiproliferative agent against the Hela cancer cell line and could be used as assistant in cancer chemotherapy (Kamlesh et al. 2004). Benzimidazole derivatives with ester groups on the benzene ring were reported for their antifungal, insecticidal, and herbicidal activities (Hisano et al. 1982; Hakan et al. 1998; Seckin et al. 2005). Furthermore, many dichlorobenzimidazoles proved a high potency against methicillin-resistant Staphylococcus aureus (MRSA) (Tuncbilek et al. 2009). Since 1985,

V.A. Mamedov, *Quinoxalines*, DOI 10.1007/978-3-319-29773-6_6

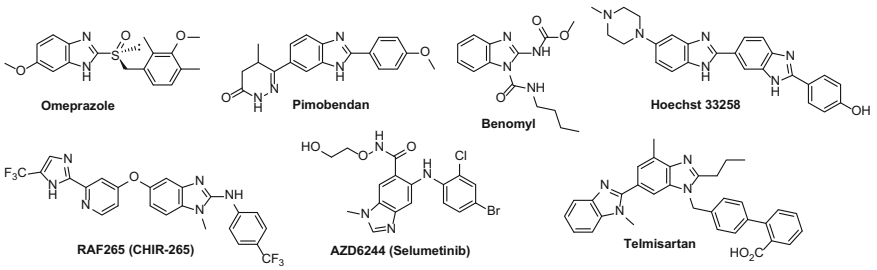


Fig. 6.1 Clinically used benzimidazoles from the current literature

benzimidazole-containing compounds have been reported as well-known anticancer agents (Ibrahim et al. 1980; Boufatah et al. 2004; Boiani and Gonzalez 2005; Piskin et al. 2009; Abdel-Mohsen et al. 2010; Shaharyar et al. 2010). The role of mammalian DNA topoisomerases as molecular targets for anticancer drugs has been recognized. Some benzimidazoles have been reported as topoisomerase inhibitors, e.g., Hoechst 33258 and Hoechst 33342 (Fig. 6.1) (Alper et al. 2003). Some widely used anticancer drugs such as RAF265 (CHIR-265; Novartis Pharmaceuticals, Basel, Switzerland) and AZD6244 (ARRY-142886; AstraZeneca, London, England) are known to contain a benzimidazole moiety. RAF265 resulted in the reduction in tumor cell growth and in tumor cell apoptosis (Wong 2009). Compound AZD6244 suppresses the growth of melanoma cells through the induction of cytostasis (Haass et al. 2008). 2-Arylbenzimidazole moiety has been defined as a pharmacophore for a new class of DNA intercalating agents (Denny et al. 1990). The importance of naphthalene benzimidazole compounds as antioxidants on hepatic cytochrome has been explored since 1997 (Ates-Alagoz et al. 1997, 2004; Ates-Alagoz and Buyukbingol 2001). On the other hand, the antiviral activity of 5-chloro and 5,6-dichloro-2-substituted benzimidazole derivatives against several viruses, e.g., influenza, human cytomegalovirus, hepatitis B virus (HBV), hepatitis C virus (HCV), and human immunodeficiency retrovirus (HIV-1) was reported (Migawa et al. 1998; Porcari et al. 1998; Budow et al. 2009). These compounds were also reported as anticancer agents against breast and prostate cancer cell lines (Andrzejewska et al. 2002) or as potential topoisomerase II inhibitors (Pinar et al. 2004). In 2010, a new series of 2-substituted benzimidazole derivatives having 5-chloro or 5-underivatized carboxylic acid group were reported to exhibit antitumor activity against hepatocellular carcinoma (HEPG2), human breast adenocarcinoma (MCF7) and human colon carcinoma (HCT 116) cell lines (Refaat 2010).

Telmisartan is a potent angiotensin II receptor antagonist used in the treatment of essential hypertension (Wienen et al. 1993; McClellan and Markham 1998; Battershill and Scott 2006). It is one of the most efficient drugs in its class, boasting the longest half-life, a high protein binding affinity, and a low daily dosage (Burnier and Brunner 2000; Cernes et al. 2011). The drug is currently marketed under the brand name of Micardis and provides additional benefits against vascular and renal

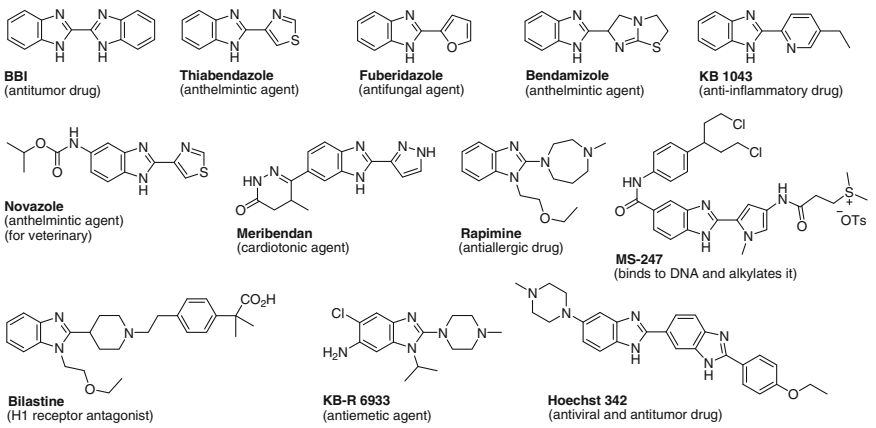


Fig. 6.2 Clinically used hetarylbenzimidazoles from the drug reference books by Mashkovskiy (2008) and Negwer (Negwer and Scharnow 2001)

damage caused by diabetes and cardiovascular disease (Benson et al. 2004; Benndorf et al. 2006; Mann et al. 2008).

The drug reference books by Mashkovskiy (2008) and Negwer (Negwer and Scharnow 2001) comprise 89 benzimidazole derivatives used in medicine. However, only 11 of them (Fig. 6.2) include other heterocyclic rings directly fused with the benzimidazole system. Probably, this is due to the fact that such compounds are hardly accessible. Indeed, the analysis of the literature data shows that the methods of synthesis of such compounds involve many steps, are laborious, and the total yields of products never exceed 20 ± 25 %.

There are two classical methods for benzimidazole synthesis, namely, coupling of 1,2-diaminobenzenes (1,2-DABs) with carboxylic acids and of 1,2-DABs with aldehydes and ketones (the Phillips-Ladenburg and the Weidenhagen reactions, respectively) (Joule and Mills 2010a). The necessity of using high temperatures (sometimes, 250–300 °C) and low yields of products limit the use of these reactions in their classical versions (Gray 1970; Hudkins 1995). Virtually, all the currently existing methods of benzimidazole synthesis represent modifications of the reactions mentioned (Balasubramaniyan et al. 1990; Grimmett 1997; Salakhov et al. 1999).

The analysis of published data has shown that the main drawback of the methods listed was their limited use in the synthesis of benzimidazole derivatives. For instance, for synthetic chemists it is a challenge to introduce a heterocycle into the position 2 of benzimidazole. In addition to the methods mentioned, examples of the formation of benzimidazole derivatives by rearrangement of heterocyclic systems are documented. Despite the fact that the publications on these reactions are much fewer as compared with the Phillips-Ladenburg and Weidenhagen reactions, they are more diverse but unfortunately not general. The generalization and systematization of data published on the rearrangement reactions will considerably facilitate

the quest of organic chemists for the methods of the synthesis of benzimidazole derivatives inaccessible by the Phillips-Ladenburg and Weidenhagen reactions. In this chapter, we will focus on recent advances in the synthesis of benzimidazoles and benzimidazolones via new rearrangements of quinoxalinones when exposed to nucleophilic reagents. However, earlier works importance will also be covered and in many cases it will include the discussions on the mechanism of the cascades.

6.2 Synthesis of Benzimidazoles

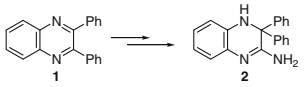
6.2.1 *Rearrangement of Quinoxalines (Historical Background)*

First example: Ogg and Bergstrom (1931) published a series of papers designed to demonstrate possible analogies between heterocyclic systems and their acyclic and alicyclic counterparts. Quinoxaline, for example, was described as an "ammono glyoxal" and 2,3-diphenylquinoxaline **1** was considered to be the heterocyclic equivalent of benzyl. In an attempt to justify this hypothesis, the authors carried out the reaction of 2,3-diphenylquinoxaline **1** with potassium amide in liquid ammonia, anticipating a reaction similar to the benzyl → benzilic rearrangement, which would lead to the formation of 2,2-diphenyl-3-aminoquinoxaline **2** (Scheme 6.1). The reaction did, in fact, lead to a new product–2-phenylbenzimidazole **3** in an approximately 30 % yield and the recovery of about 60 % of unchanged 2,3-diphenylquinoxaline **1** (Taylor and McKillop 1965).

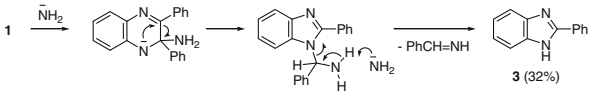
The formation of 2-phenylbenzimidazole **3** from 2,3-diphenylquinoxaline **1** and potassium amide must involve the initial addition of an amide ion at the C(2) carbon atom, as Ogg and Bergstrom (1931) had postulated, but with subsequent ring contraction, presumably with the elimination of benzylidenimine. This would result in the observed product **3**, rather than the phenyl migration of the benzyl acid-rearrangement type (Scheme 6.2).

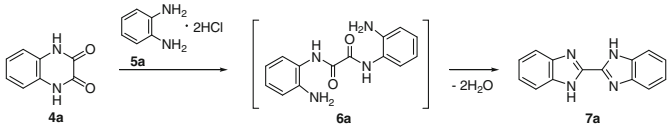
Attempts to effect the ring contraction of 2,3-diphenylquinoxaline **1** to 2-phenylbenzimidazole **3** with other bases (KOH in H_2O or EtOH, NaOH in MeOH, NaH in toluene) were unsuccessful. The efficacy of KNH_2 appears to be specific.

Scheme 6.1 Proposed benzyl → benzilic rearrangement



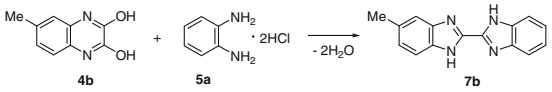
Scheme 6.2 Proposed mechanism of the rearrangement





Scheme 6.3 Synthesis of 2,2′-bibenzimidazole

Scheme 6.4 Synthesis of an unsymmetrically substituted 2,2′-bibenzimidazole



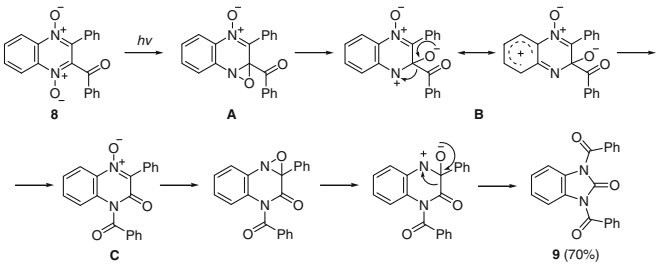
Second example: Quinoxaline-2,3(1*H*,4*H*)-dione **4a** with 1,2-DAB dihydrochloride was shown to interact with the formation of the highly labile compound **6a**. As a result of "ammonolysis" this compound was spontaneously dehydrated and cyclized to form compound **7a** (Scheme 6.3) (Lane 1955).

This reaction sequence has been used for the preparation of an unsymmetrically substituted 2,2′-bibenzimidazole, since 2,3-dihydroxy-6-methylquinoxaline **4b** and 1,2-DAB dihydrochloride reacted to form 5-methyl-2,2′-bibenzimidazole **7b** (Scheme 6.4) (Lane 1955).

Third example: Exposure to sunlight of a methanolic solution of 2-benzoyl-3-phenylquinoxaline di-*N*-oxide **8** in a Pyrex flask for 12 h, resulted in the precipitation of 1,3-dibenzoylbenzimidazolone **9** in 70 % yield (Haddadin and Issidorides 1967; Jarrer et al. 1976). This rearrangement can be envisaged to involve two nitrone functions in one molecule. It is generally accepted that the irradiation of nitrones leads to oxazirane intermediates which may undergo further thermal and photochemical rearrangements (Krohnke 1957; Splitter and Calvin 1965; Streith and Sigwatt 1966). Hence, it is reasonable to assume that, on irradiation, **8** is transformed into the isomeric oxazirane **A**. Considering the mechanism for the formation of **9** from oxazirane **A**, the authors favor intermediate **B** arising from thermal heterolytic N–O bond fission of the oxirane ring, as advanced by Splitter and Calvin (1965) for the thermal decomposition of 2,3-diaryloxaziranes. Intermediate **B**, in which the positive charge on the nitrogen is delocalized by resonance with the adjacent aromatic ring, may then be postulated to undergo 1,2-benzoyl migration to electron-deficient nitrogen giving **C**, the driving force for this shift being supplied by the negative charge on the oxygen (Scheme 6.5). Applying of this mechanism on the nitrone system at positions 3 and 4 would then the observed product **9** by ring contraction.

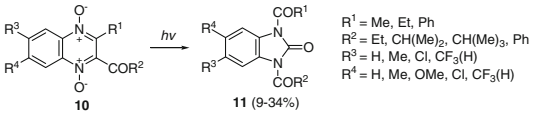
Ring contraction also occurs in irradiation of quinoxaline di-*N*-oxide of the type **10**, the product of the reaction being a 1,3-disubstituted benzimidazolone **11** (Scheme 6.6) (Jarrer et al. 1976).

Fourth example: Quinoxaline 1-oxides **12a**–**i**, bearing a substituent at C(2), a carbonyl at C(3), and a free hydrogen at N(4), when heated with acetic anhydride, are transformed into l-acetyl-3-acetyl-2-benzimidazolinones or 1,3-diacetyl-2-benzimi-

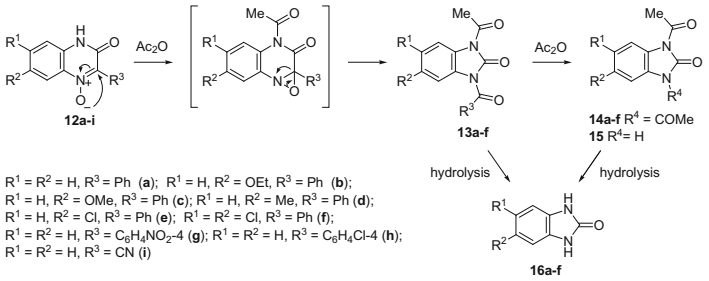


Scheme 6.5 Proposed mechanism of the rearrangement of 2-benzoyl-3-phenylquinoxaline di-*N*-oxide when exposed to sunlight

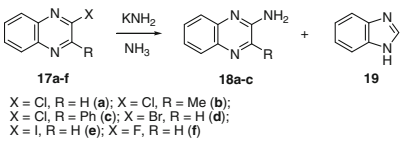
Scheme 6.6 Ring contraction of quinoxaline di-*N*-oxide when exposed to light



dazolones depending on the nature of substituents at C(2), C(6), and C(7) (Ahmad et al. 1968). For example, when 3-hydroxy-2-phenyl- (**12a**), 7-ethoxy-3-hydroxy-2-phenyl- (**12b**) and 3-hydroxy-7-methyl-2-phenyl-quinoxaline 1-oxide (**12d**) on being heated with acetic anhydride under reflux for 4 h, they yield l-acetyl-3-benzoyl-2-benzimidazolone (**13a**) and its 5-ethoxy- and 5-methyl-l-acetyl-3-benzoyl derivatives **13b** and **13d**, respectively, which on hydrolysis with aqueous alkali lost their acetyl and benzoyl groups and yielded benzimidazolone **16a** and its 5-ethoxy- (**16b**) and 5-methyl- (**16d**) derivatives (Scheme 6.7). 3-Hydroxy-2-(4-nitrophenyl) quinoxaline 1-oxide **12g** remained unchanged even on prolonged heating under reflux with acetic anhydride. However, when the two reactants were heated together in a sealed tube at 180 °C for 12 h, the products of the reaction were 1,3-diacetyl- and l-acetyl-2(3*H*)-benzimidazolones **14a** and **15** with 4-nitrobenzoic acid. Similarly, 2-cyano-3-hydroxyquinoxaline 1-oxide **12i** failed to react with acetic anhydride under ordinary conditions of reflux. However, in a sealed tube at 180 °C, it gave 1,3-diacetyl-2-benzimidazolone **14a** as well.



Scheme 6.7 Proposed mechanism of the rearrangement of 3-hydroxy-2-R-quinoxaline 1-oxides when heated under reflux with acetic anhydride



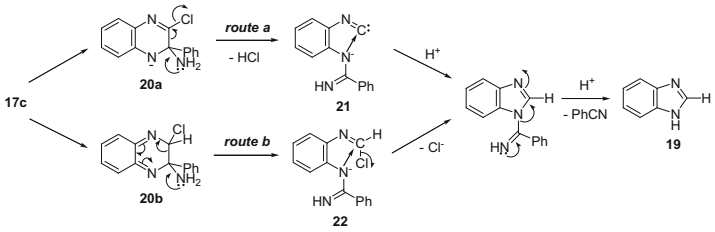
Scheme 6.8 The reaction of 2-haloquinoxalines with potassium amide

Fifth example: In every case when the 2-chloroquinoxaline **17a-c** was heated with potassium amide in liquid ammonia at low temperature, benzimidazole **19** was formed as well as the corresponding 2-aminoquinoxalines **18a-c** (Scheme 6.8) (Lont and Van der Plas 1972). This indicates that the ring contraction is not prevented by the presence of a substituent at position 3 (Me or Ph), and that it is the carbon atom 3 in the quinoxaline ring which is eliminated. Considering the mechanism of this ring contraction it seems likely that an initial attack of the amide ion at position 3 takes place, which results in the intermediate **20** (Scheme 6.9) (Lont and Van der Plas 1972).

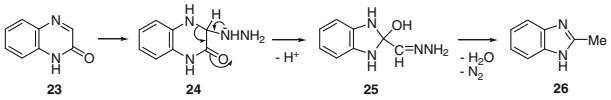
At present, it is yet unclear whether in the course of this reaction isonitrile **21** (Scheme 6.9, route *a*) or iminochloride **22** (Scheme 6.9, route *b*) is involved. It is tentatively suggested that this ring contraction takes the course shown below (Scheme 6.9). The formation of a nitrile has been confirmed by the fact that with **17a** it is possible to isolate benzamidine, which is probably formed by the addition of potassium amide to benzonitrile.

It should be pointed out that with 2-chloroquinoxaline the main product is benzimidazole, and only some 2-aminoquinoxaline is formed. Under these conditions 2-bromo- (**17d**) and 2-iodo- (**17e**) quinoxaline are almost exclusively converted into benzimidazole, whereas with 2-fluoroquinoxaline **17f** only a trace of benzimidazole is formed (Lont and Van der Plas 1972).

Sixth example: It has been found (Cheeseman and Rafig 1971) that hydrazinolysis of quinoxalin-2(1*H*)-one **23** in boiling 50 % aqueous hydrazine leads to the formation of 2-methylbenzimidazole **26**. This interesting reaction has again demonstrated the strong tendency of hydrazine to bring about ring transformation. This is assumed to occur by an initial addition of hydrazine at the C=N bond of **24**, thus the 3,4-addition analogues to addition reactions in 6- and 7-oxopteridines with nucleophilic reagents (Albert and McCormack 1965). As indicated, the ring

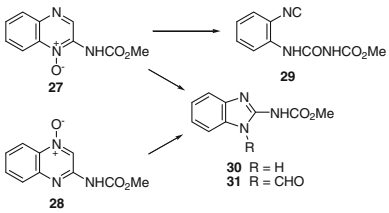


Scheme 6.9 Proposed mechanism of the rearrangement of 2-chloroquinoxalines into benzimidazole when exposed to potassium amide in liquid ammonia

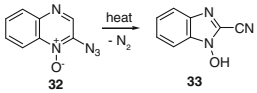


Scheme 6.10 Hydrazinolysis of quinoxalin-2(1*H*)-one

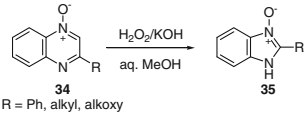
Scheme 6.11 Photolysis of the quinoxalin-2-ylcarbamate *N*-oxides



Scheme 6.12 Thermolysis of 2-azidoquinoxaline 1-oxide



Scheme 6.13 Oxidation of quinoxaline 4-oxides



contraction into **25**, and the reductive conversion of the –HC=N–NH_2 into a methyl group by a Wolff–Kishner type process, together with dehydration, gives **26** (Scheme 6.10).

Seventh example: Photolysis of the quinoxalin-2-ylcarbamate *N*-oxides **27** and **28** in various solvents (e.g., methanol) gives the benzimidazol-2-ylcarbamates **30** and **31**. Under acidic conditions the 1-oxide **27** yields the isonitrile **29** (Scheme 6.11) (Burrell et al. 1973).

Eighth example: A further case of ring contraction has been reported on the thermolysis of 2-azidoquinoxaline 1-oxide **32** when 2-cyano-1-hydroxybenzimidazole **33** is formed (Scheme 6.12) (Abramovitch and Cue 1973).

Oxidation of 2-phenylquinoxaline 4-oxide **34** with a 30 % aqueous hydrogen peroxide in acetic acid (Hayashi and Iijima 1962) or formic acid (Ahmad et al. 1966) gives the 1,4-dioxide, which on reduction with sulfurous acid in methanol yields 2-phenylquinoxaline 1-oxide. However, treatment of the 4-oxide **34** with a 30 % aqueous hydrogen peroxide in methanol and the presence of potassium hydroxide furnishes 2-phenylbenzimidazole 3-oxide **35**. This is a general reaction of 2-alkyl- and 2-alkoxyquinoxaline 4-oxide (Scheme 6.13) (Hayashi and Miura 1967).

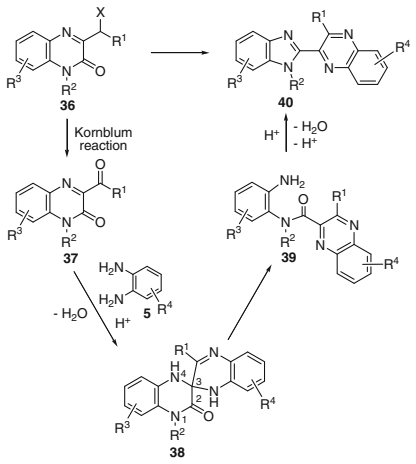
As evident from the above eight examples of rearrangement of quinoxaline derivatives, the first two and the sixth lead to the 2-substituted benzimidazoles, and

the third and fourth result in the *N*-substituted benzimidazolones. All of them except the last one are special cases, i.e., implemented as the special representatives of the benzimidazole derivatives. As for the fourth example, the possibility of this reaction is limited to the synthesis of the derivatives of benzimidazolones with substituents only on the benzene ring. As a result of rearrangement they are eliminated as substituents at position 3 of the starting compounds. Thus, none of these methods of the synthesis of benzimidazole derivatives can compete with the classical Phillips-Ladenburg and Weidenhagen reactions.

6.2.2 *Principles of the Method*

Quinoxalin-2(1*H*)-ones **37** can be converted into substituted benzimidazoles **40** following the reaction sequence, first reported in 2000 (Kalinin et al. 2000, 2007; Mamedov et al. 2004, 2008a, 2010a), and shown in Scheme 6.14. Firstly, 3-(α-chloro (or bromo)benzylquinoxalin-2(1*H*)-ones **36** are oxidized with the Kornblum type reactions (Mamedov et al. 2002, 2014a; Gorbunova and Mamedov 2006) or the direct oxidation of 3-benzyl (or alkyl) quinoxalin-2(1*H*)-ones **36** with the help of CrO_3 in acetic acid with water (Mamedov et al. 2005a; Kalinin et al. 2007) to give 3-aroyl- or 3-alkanoylquinoxalin-2(1*H*)-ones **37**. 3-Aroyl- or 3-alkanoyl-quinoxalin-2(1*H*)-ones **37** react with 1,2-DABs **5** to give the spiro-quinoxalinone derivative **38**. The spiro-quinoxalinone derivative **38** is then heated in acetic acid to give the benzimidazole derivative **40** through the proceeding cascade reactions involving: a) acid-catalyzed ring-opening of spiro-compound **38** with the formation of quinoxaline derivative **39**, b) the intramolecular nucleophilic attack by the amino moiety on the carbonyl group leading to the formation of the final product **40** with the elimination of water. Practically for every case the spiro-compound **38** can be

Scheme 6.14 The reaction sequence of the rearrangement



isolated and individually characterized, but the quinoxaline derivative **39** is only rarely isolated. The sequence is thus based on the combination of the following facts:

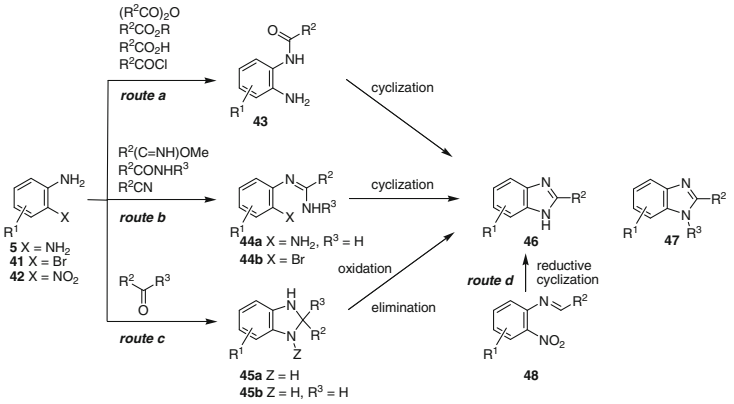
(i) The presence of the carbonyl group at position 3 of quinoxalin-2(1*H*)-ones **37**, according to the principle of Ogg and Bergstrom (1931) allows to consider them as the hetero analogues of α-diketones.
(ii) The susceptibility of these systems to the reactions of the usual α-diketones, according to the Hinsberg reaction (Hinsberg 1884) involves spiro-quinoxaline derivatives with at least one mobile hydrogen atom in the spiro-forming component (Kalinin et al. 2000, 2007; Mamedov et al. 2004, 2006, 2008a, 2010a).
(iii) The susceptibility of the spiro-quinoxaline derivatives **38** to the acid-catalyzed ring-opening with the formation of quinoxaline derivatives **39**, and the intramolecular ring-closure reaction with the formation of benzimidazole derivatives **40**.

In the reactions discussed above aroyl- and alkanoylquinoxalinones were dealt with as heteroanalogues of α-diketones. Following this line of thought, assume the 3-(α-haloalkyl)- and 3-(α-halobenzyl)quinoxalin-2(1*H*)-ones, 3-(α-aminobenzyl) quinoxalin-2(1*H*)-ones and 3-arylacylidene-3,4-dihydroquinoxalin-2(1*H*)-ones to be analogues of α-haloketones, α-aminoketones and β-diketones, respectively.

6.2.3 Advantages of the Method

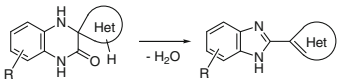
The present method for the synthesis of substituted benzimidazoles starting from quinoxalin-2(1*H*)-one derivatives has the following characteristics or distinct advantages over the previously used routes (the Phillips-Ladenburg and the Weidenhagen reactions) or their many variations.

(A) First, the acid-catalyzed rearrangement of spiro-quinoxalinone derivative **38** through the *o*-aminoanylide quinoxaline 2-carboxylic acid **39** requires a milder reaction condition and provides almost quantitative yields of benzimidazole derivative **40** (Scheme 6.14) than do the most popular approaches generally involving the condensation of an arylenediamine with a carbonyl equivalent (Scheme 6.15). For example, the reaction of 1,2-DABs with carboxylic acid or acid chloride results in intermediate amide **43**. In order to produce benzimidazole **46** the latter in turn could undergo a cyclodehydration reaction at elevated temperatures under strong acidic or alternatively under harsh dehydrating conditions, often, (Scheme 6.15, route *a*). Similarly, esters, lactones, and anhydrides could generate benzimidazoles via the cyclization of amide **43**, although given the rather harsh reaction conditions required and the poor diversity profile of the final products their scope might be limited. For



Scheme 6.15 Common strategies for the synthesis of benzimidazoles

Scheme 6.16 Schematical presentation of the rearrangement



instance, the reaction of 1,2-DABs with aliphatic esters and lactones involves the use of strong mineral acids such as hydrochloric acid, sulfuric acid, hot glacial acetic acid, or polyphosphoric acid under very high temperatures, i.e., conditions not fully compatible with a broad range of functional groups and desirable substrates. Aromatic esters require temperatures up to 250–300 °C, thus rendering the synthesis of 2-arylbenzimidazoles almost impractical (Gray 1970). However, the reaction of aromatic esters with 1,2-DABs under the Weinreb conditions could provide access to 2-arylbenzimidazoles (Hudkins 1995). In the class of acid anhydrides of monobasic acids, only acetic anhydride has been practically used in the preparation of 2-methylbenzimidazoles. Cyclic anhydrides of dibasic acids have also been used in the synthesis of benzimidazoles, although high temperatures and strong acids are usually necessary to convert the intermediate *N*-(*o*-aminophenyl)-imide into the desired benzimidazole (Balasubramaniyan et al. 1990; Salakhov et al. 1999). In addition, a mixture of regioisomeric benzimidazoles could result from the reaction of nonsymmetric anhydrides with arylenediamines.

In the presence of HCl the reaction of 1,2-DABs with amides (Von Niementowski 1897) and nitriles (Hölljes and Wagner 1944) at 200–250 °C could also afford 2-substituted benzimidazoles with the general structure **46** via the cyclization of intermediate amidine **44a** (Scheme 6.15, route *b*). Alternatively, upon the formation and subsequent cyclization of amidine **44a** under milder conditions (King and Acheson 1949) the reaction of 1,2-DABs

with an imidate could afford benzimidazole **46** as well. Although the imidate route could provide access to a diverse set of 2-substituted benzimidazoles starting from several commercially available aliphatic and aromatic nitriles, the hydroscopic nature of the intermediate imidates might be of concern, particularly in a high throughput setup. The palladium-catalyzed intramolecular *N*-arylation reaction of the *o*-bromophenylamidine precursors of type **44b**, resulting from the assisted $POCl_3$ condensation of bromoaniline **41** and an amide, has been recently developed providing entry to *N*-substituted benzimidazoles with the general structure **47** (Brain and Brunton 2002; Brain and Steer 2003). Despite the somewhat harsh conditions required to generate the intermediate amidine precursors, this method successfully addresses the regioselective synthesis of *N*-substituted benzimidazoles which currently constitutes a limitation of many other approaches.

Aldehydes and, to a lesser extent, ketones can also afford benzimidazoles when condensed with 1,2-DABs (Scheme 6.15, route *c*). Although the reaction of ketones with 1,2-DABs in the presence of HCl at 250–300 °C can yield benzimidazole **46** by the aromatization of intermediate benzimidazoline **45a**, their use has been rather limited (Elderfield and Kreysa 1948; Wright 1951). Furthermore, since the aromatization of benzimidazoline **45a** occurs via the elimination of an alkyl group, a mixture of benzimidazoles could result from nonsymmetric ketones. Alternatively, aldehydes have been used more extensively in the preparation of 2-substituted benzimidazoles according to the Weidenhagen's method (1936). For example, condensation of 1,2-DABs with an aldehyde, followed by the oxidation of the intermediate benzimidazoline **45b** could afford benzimidazole **46** as well. While the oxidation can proceed spontaneously by disproportionation, this can lead to the occurrence of side products. Oxidative methods usually require heating in nitrobenzene or DMF at elevated temperatures, as well as the use of metal ions, iodine, organic oxidants, or inorganic sulfites when heated (Beaulieu et al. 2003). However, one mild set of oxidation conditions utilizing oxone has been recently described for the synthesis of *N*-substituted and N–H benzimidazoles (Beaulieu et al. 2003).

A method which could be a viable alternative to the widely used 1,2-DAB based synthetic methods, although according to their knowledge, not studied in depth to date employs the reductive cyclization of *N*-benzylidene-2-nitroanilines **48** (R^2 = Ar), prepared from *o*-nitroaniline **42** and benzaldehydes (Scheme 6.15, route *d*). Triethylphosphite (Cadogan et al. 1970), triruthenium dodecacarbonyl (Tollari et al. 1994) in the presence of carbon monoxide, and recently, phenylmagnesium chloride (Dohle et al. 2003) have been successfully utilized as the reducing agents for this transformation. The reaction presumably proceeds via an in situ aryl nitro reduction, followed by an intramolecular cyclization (Sundberg 1965; Sundberg and Yamazaki 1967; Dohle et al. 2003), to afford benzimidazole **46** (R^2 = Ar). Even though this

strategy could obviate the preparation and isolation of the intermediate 1,2-DABs, especially those that are known to be water-soluble or prone to air-oxidation, it would still require the preparation and isolation of the corresponding *N*-benzylidene-2-nitroanilines **48** prior to subjecting them to cyclization conditions.

(B) Second, the synthesis of substituted benzimidazoles can be accomplished starting from the quinoxalin-2(1*H*)-one derivative **36** easily available with the use of various preparatively simple ways under mild conditions from corresponding substituted 1,2-DABs and pyruvates. In doing so as a result of the rearrangement substituents of the benzene ring of quinoxaline system appeared to be on the benzene ring of the benzimidazole ring. As a result of the rearrangement the substituent R^2 at position N(1) of the quinoxalin-2(1*H*)-one system transfer to the *N* atom of benzimidazole system.

(C) The route **36**–**40** clearly shows that a benzyl (or haloalkyl) group can be converted (by use of the Kornblum reaction) into a ketone group. Thereby compound **37** is due to the imine group and the newly introduced ketone group is formally converted into the hetero analogue of α-diketone, necessary for the synthesis of quinoxaline by the Hinsberg reaction (Hinsberg 1884, 1887).

(D) As can be seen from the reaction depicted in Scheme 6.14, the key step in this case is the formation of spiro-compound **38**. As a result of the cascade reaction this compound is transformed into a benzimidazole derivative **40**, containing a heterocyclic system. This system acts as a spiro-fragment in the intermediate compound **38**. The result makes it possible to propose the main principle for this rearrangement. ***Any of the spiro-derivatives of 1,2,3,4-tetrahydroquinoxalin-3-one with at least one mobile hydrogen atom in their spiro-forming components can be converted into the benzimidazole derivative with the spiro-forming component at position 2*** (Scheme 6.16) (Mamedov et al. 2010b, 2011a).

(E) The understanding of the reaction mechanism makes it possible for them to make a bold assumption. As can be seen from Fig. 6.3, all the reactions of aroyl- and alkanoylquinoxalines when interacting with 1,2-DABs at the initial stage behave as hetero analogues of α-diketones, that is, as iminoketones (see Sects. 6.4 and 6.10). Then there arises the problem, why other quinoxaline derivatives with certain substituents do not behave like α-haloketones **49** (see Sect. 6.5), β-diketones **50** (see Sect. 6.6), α-aminoketones **51** (see Sect. 6.7), methyl ketones **52** (see Sect. 6.8), aromatic *o*-aminoaldehydes (or ketones) **53** (see Sect. 6.9), etc.

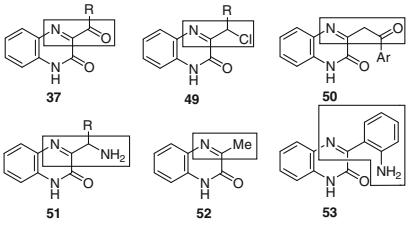


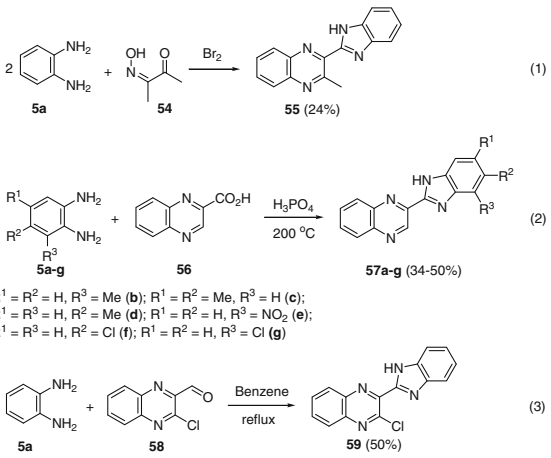
Fig. 6.3 Schematical presentation of the quinoxalin-2-ones as functional ketones

6.3 Synthesis of 2-(Benzimidazol-2-yl)quinoxalines with no Use Rearrangements

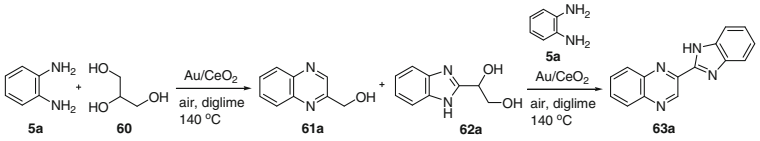
6.3.1 Gold Catalysis for Synthesizing 2-(Benzimidazol-2-yl) quinoxaline Derivatives from Glycerol and 1,2-Diaminobenzenes

Methods for the synthesis of these hetarylquinoxalines are limited. An option involves the reaction of the 1,2-DAB **5a** with 3-hydroxyimino-2-butanone **54** and bromine in a one-pot reaction (Scheme 6.17, Eq. 1) (Sarodnick and Kempter 1983). Another possibility is to react 1,2-DABs **5a–g** with quinoxalin-2-carboxylic acid **56**, but this synthetic route needs to be performed in a polyphosphoric acid media at 200 °C (Scheme 6.17, Eq. 2) (Mizutani et al. 1994; Novellino et al. 2005). A third route is to react the 1,2-DAB **5a** with quinoxalin-2-carboxaldehyde **58** in benzene at reflux temperature (Scheme 6.17, Eq. 3) (Lippmann and Shilov 1984). In all three cases, the yield of the target product remains very low.

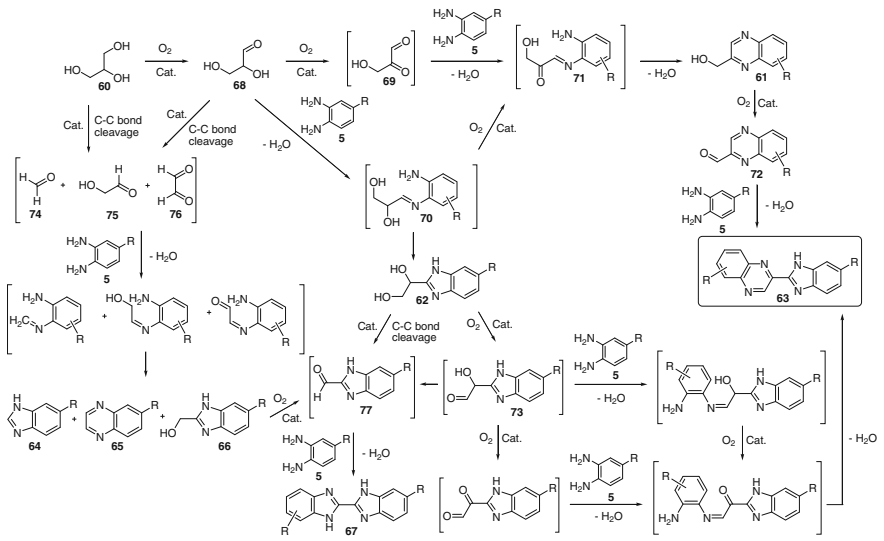
A gold catalyst (Au/CeO_2) was used to synthesize benzimidazolylquinoxalines by two novel methods in a multistep one-pot methodology (Climent et al. 2013). The first method involved the oxidative coupling of glycerol **60** with 1,2-DAB **5a** performed at 140 °C using diglyme as a solvent and lead to the benzimidazolylquinoxaline compound **63a** through the formation of intermediates **61a** and **62a** (Scheme 6.18). In this case, the benzimidazolylquinoxaline possesses the same substituents in both heterocycles. Then, with the aim to expand the synthetic scope, an alternative route that allows combining different substituents in both heteroaromatic moieties was designed.



Scheme 6.17 Benzimidazolylquinoxaline synthesis routes according to the references (Sarodnick and Kempter 1983; Lippmann and Shilov 1984; Mizutani et al. 1994; Novellino et al. 2005)



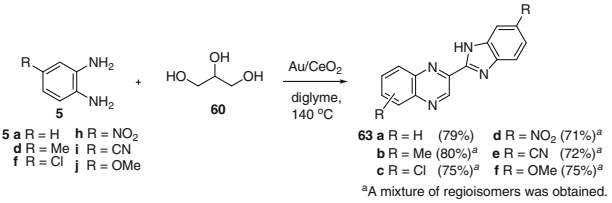
Scheme 6.18 New one-pot two-step process for the synthesis of benzimidazolylquinoxalines starting from glycerol



Scheme 6.19 Proposed benzimidazolylquinoxalines synthesis mechanism starting from 1,2-DAB derivatives and glycerol

However, at the beginning of the reaction, the quinoxalin-2-ylmethanol **61a**, formed by oxidative coupling between glycerol **60** and 1,2-DAB **5a**, and the 1-(1*H*-benzo-[*d*]imidazol-2-yl)ethane-1,2-diol **62a**, which could be produced through the oxidation of one of the primary alcohol groups of glycerol and subsequent coupling with 1,2-DAB **5a**, were the predominant products (Scheme 6.18). Both compounds (**61a** and **62a**) exhibited a primary and unstable character and after 1 h of reaction, the concentrations of both intermediates began to decrease, which was caused by their conversion into 2-(1*H*-benzo[*d*]imidazol-2-yl)quinoxaline **63a**, produced through oxidation-cyclization of **61a** and **62a** with another 1,2-DAB molecule **5a**. Other by-products such as 1*H*-benzo[*d*]imidazole **64a**, quinoxaline **65a**, (1*H*-benzo [*d*]imidazol-2-yl)methanol **65a** and 1*H*,1′*H*-2,2′-bibenzo[*d*]-imidazole **66a** were also detected in the reaction media (Scheme 6.19).

The proposed mechanism (Scheme 6.19) of the processes involves the oxidation of glycerol **60** to glyceraldehyde **68** and subsequently to the dicarbonyl compound **69**. Both compounds can condense with 1,2-DAB to produce the imine intermediates **70** and **71**, with **70** converted into product **71** by fast oxidation of the



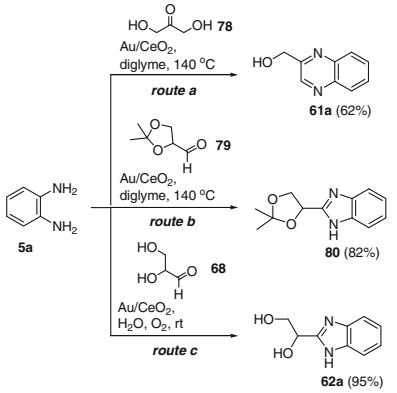
Scheme 6.20 Synthesis of benzimidazolylquinoxaline derivatives starting from 1,2-DABs and glycerol with Au/CeO_2 as a catalyst

remaining hydroxyl group. Later, product **71** follows a condensation reaction to yield hydroxymethylquinoxaline intermediate **61**, which can be further oxidized to 2-carboxaldehydequinoxaline **72**, which couples with another molecule of 1,2-DAB to reach the benzimidazolylquinoxaline derivative **63**. Moreover, the imine intermediate **71** can result in the dihydroxybenzimidazole intermediate **62**, which through a subsequent oxidative coupling with 1,2-DAB produces the benzimidazolylquinoxaline derivative **63**. On the other hand, the formation of the by-products detected by gas chromatography could be explained by the oxidative cleavage of glycerol **60**, glyceraldehyde **68**, the dihydroxybenzimidazole intermediate **62**, and the α-hydroxycarbonylbenzimidazole intermediate **73** into different carbonyl compounds such as **73**, **74**, **75**, and **76**. This is followed by the coupling with 1,2-DAB to produce the by-products **64**, **65**, **66**, and **67** through cyclization in minor amounts.

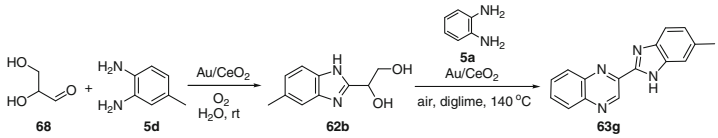
As can be seen in Scheme 6.20, good yields to benzimidazolylquinoxaline derivatives were obtained. However, with electron-withdrawing substitutents such as nitro, chloro or nitrile groups, the yields of quinoxaline derivatives were slightly lower with respect to those of 1,2-DAB or with respect to 1,2-DABs with electron-donating substituents such as methyl and methoxy. Besides that in all these cases the reactions proceed with the formation of regioisomers of benzimidazolylquinoxalines.

To develop a method for the synthesis of the 2-benzimidazolylquinoxaline derivatives with different substituents in the benzimidazole and quinoxaline fragments the conditions for the formation of the assumed intermediate products of the reaction, namely hydroxymethylquinoxaline **61a**, 1-(1*H*-benzo[*d*]imidazol-2-yl) ethane-1,2-diol **62a**, and its protected derivative **80** were investigated (Scheme 6.21) (Climent et al. 2013).

After optimization of the reaction conditions with the different substrates, the results presented in Scheme 6.22 revealed that only the reaction between glyceraldehyde and 1,2-DAB (Scheme 6.21, route *c*) in the presence of Au/CeO_2, oxygen pressure, and at room temperature, produced the benzimidazole intermediate **62** with high selectivity with complete conversion. Therefore, the synthesis of the benzimidazole intermediate from glyceraldehyde and 1,2-DAB derivative was chosen as the optimum first step of the reaction.



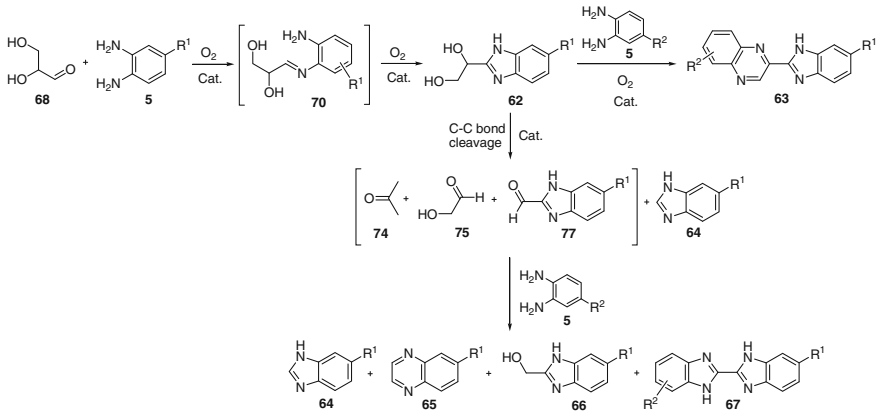
Scheme 6.21 Possible synthetic routes to yield the intermediate quinoxaline **60a** or benzimidazole **79**, **61a**



Scheme 6.22 New one-pot two-step process to produce benzimidazolylquinoxalines starting from glyceraldehyde

This second process involves two sequential steps with very different reaction conditions. In the first one, glyceraldehyde is coupled with an 1,2-DAB derivative in the presence of Au/CeO_2 to produce the intermediate **62** under very mild reaction conditions (room temperature, 3 bar O_2, and water as a solvent). Once the complete conversion of glyceraldehyde is achieved, a solution of the second 1,2-DAB molecule **5d** in diglyme is added, and the temperature is increased to 140 °C while the water is removed by a Dean-Stark system. The main product observed under these conditions is the benzimidazolylquinoxalines **63g** (Scheme 6.22), which is formed by oxidative coupling between the intermediate **62** and the 1,2-DAB molecule **5d** (Climent et al. 2013). Both routes were applied to the synthesis of different benzimidazolylquinoxaline derivatives, which were obtained in yields between 60 and 80 %.

As can be seen from the reaction mechanism (Scheme 6.23) and from the data in the Scheme 6.20, this method cannot be used effectively in the case of the synthesis of substituted derivatives of 2-benzimidazolylquinoxalines, as the reactions of mono-substituted derivatives of 1,2-DAB proceed with the formation of the mixtures of regioisomers, which is difficult to separate. The problem is further complicated when using the diversely-substituted derivatives of 1,2-DAB. The use of expensive (Au) and environmentally unsafe (CeO_2) catalyst also limits the possibilities of this method.

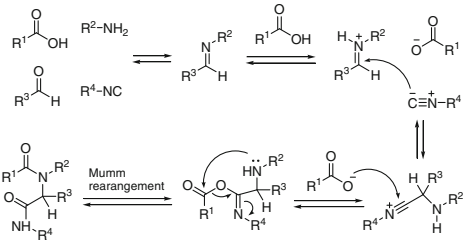


Scheme 6.23 Proposed benzimidazolylquinoxalines synthesis mechanism from 1,2-DABs and glyceraldehyde

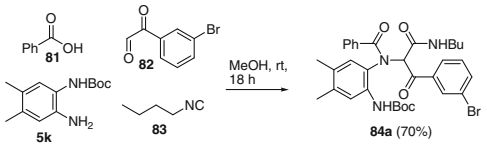
6.3.2 *Synthesis of Quinoxalines and 2-(Benzimidazol-2-yl) quinoxalines via the Isocyanide Based Multicomponent Reactions (IMCRs)*

IMCRs are viewed in many areas as a principal field of study for the generation of both new chemotype diversity and preferred methodologies to afford known heterocycles (Hulme and Gore 2003; Dömling 2006; Hulme and Dietrich 2009; El Kaim and Grimaud 2009; Banfi et al. 2010; Xu et al. 2012a, b). Specifically, the venerable Ugi reaction, Scheme 6.24, has proved extremely versatile in enabling access to libraries of small molecules through a variety of strategies that encompass post-condensation modifications of the Ugi adduct and exploitation of the "diversity of nucleophiles" able to trap out the intermediate "nitrilium ion" of the Ugi reaction in both intra- and intermolecular modalities. Efforts by several groups have seen concise methodologies developed that enable access to diazepines (Hulme et al. 1998a; Huang et al. 2012), ketopiperazines (Hulme et al. 1998b, c), imidazolines (Hulme et al. 1999), β-lactams (Hulme et al. 2000a) and hydantoins, to name but a few (Hulme et al. 2000b; Pakornwit and Krasivan 2014). As such, the synthetic routes fall into the realm of UDC methodology (Ugi/Deprotect/Cyclize) where the final ring closing event is mediated through amide bond formation (Hulme and Gore 2003; Xu et al. 2012a).

When 3-bromophenyl glyoxaldehyde **82** and *N*-Boc-(4,5-dimethyl)-1,2-DAB **5k** were used instead of amine and aldehyde components in the above reaction the process proceeded smoothly in methanol at ambient temperature resulting in the Ugi adduct **84** in a 70 % yield (Scheme 6.25). The simple TFA treatment of **84**

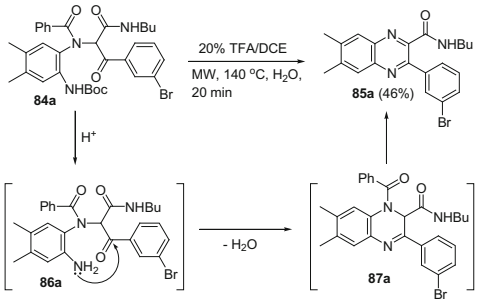


Scheme 6.24 Mechanism of the four-component Ugi reaction



Scheme 6.25 Four-component one-pot Ugi reaction

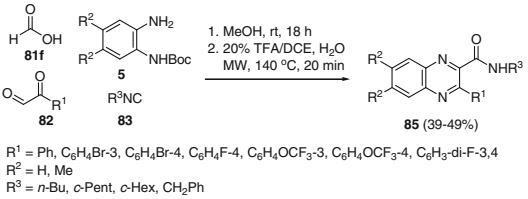
Scheme 6.26 Conversion of Ugi adduct into quinoxaline **85a** via intermediates **86a** and **87a**



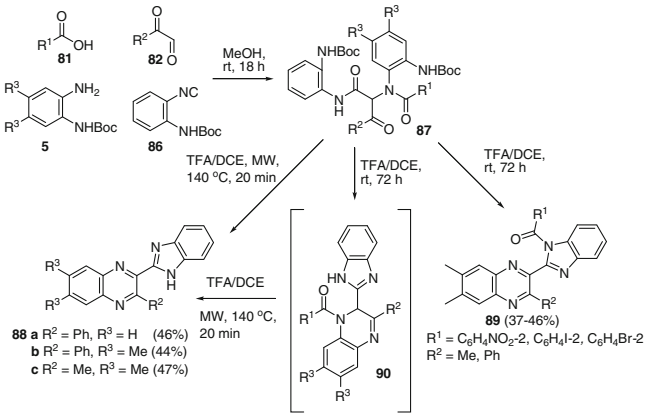
delivers **85a** in good yield, representing the first reported synthesis of quinoxalines derived in one step from the Ugi reaction, postulated to proceed in an unexpected fashion through intermediates **86** and **87** (Scheme 6.26) with the loss of a benzoyl (Hulme et al. 1998a; Huang et al. 2012). Interestingly, the final product is significantly different from its Ugi precursor and as such, the methodology provides a unique opportunity to rapidly access such a diversity space.

One-pot procedure translated into a higher overall yield of **85a** (46 %) when compared to that of the two-step process (34 %) (Scheme 6.26) (Ayaz et al. 2014).

Exploring the scope of the reaction, various aldehydes, 1,2-DABs and isonitriles were used to furnish a set of diversified quinoxalines and gratifyingly, the transformation worked equally well for all inputs (Scheme 6.27) (Ayaz et al. 2014).



Scheme 6.27 Study of the reaction scope



Scheme 6.28 Synthesis of 2-benzimidazolylquinoxalines

Using the same reaction conditions, it was envisioned that the use of isonitrile **86** (*o*-*N*-Boc-phenylisonitrile) (Gunawan et al. 2012) would facilitate access to 2-benzimidazolylquinoxalines **88**. The Ugi reaction proceeded smoothly and upon microwave irradiation of Ugi products **87** with a 20 % TFA/DCE, 2-benzimidazolylquinoxalines **88a–c** were obtained in good yield (Scheme 6.28) (Ayaz et al. 2014). 2-Benzimidazolylquinoxaline products **89** were observed when utilizing bulky *o*-substituted aromatic acids which had retained the benzoyl group through an internal acyl-transfer from the nitrogen derived from the original Ugi amine input to the adjacent benzimdazole.

Low yields of the desired products (39–49 % in the cases of quinoxaline derivatives, and 37–46 % in the case of 2-benzimidazolylquinoxalines) and the limited availability of mono- and diversely-substituted derivatives of *o*-*N*-Boc-phenylisonitrile **86** and *N*-Boc-1,2-DAB limits the possibility of using this approach to the synthesis of variously substituted by quinoxaline and benzimidazole bicyclic derivatives of quinoxalines and 2-benzimidazolylquinoxalines.

6.4 Synthesis of 2-Hetarylquinoxalines via Rearrangements (Use of 3-Aroyl-, 3-Alkanoyl- and 3-Hetaroylquinoxalin-2(1*H*)-ones as Analogues of α-Diketones)

6.4.1 Synthesis of 2-(Benzimidazol-2-yl)quinoxalines and Their Aza-Analogues

One of the common reactions of α-diketones in the chemistry of heterocycles is the Hinsberg reaction (Hinsberg 1884), i.e., the synthesis of quinoxalines by the interaction of 1,2-DABs with α-dicarbonyl compounds.

Thus a series of reactions according to Hinsberg were carried out.

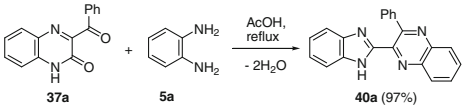
The reaction of quinoxalin-2-one **37a** (the schematical presentation of the 3-aroyl-, 3-alkanoyl- and 3-hetaroylquinoxalin-2(1*H*)-ones as analogues of α-diketones has been shown in Sect. 6.2.3(E) (see Fig. 6.3, structure **37**)) with 1,2-DAB **5a** in boiling acetic acid leads to the corresponding 2-benzimidazolylquinoxaline **40a** in a 97 % yield (Scheme 6.29) (Kalinin 2000; Kalinin et al. 2000).

Tables 6.1 and 6.2 show that a variety of quinoxalinones **37a-r** and 1,2-DABs **5a**, **d**, **h** are compatible with these reaction conditions, with diverse 2-benzimidazolyl substituted quinoxalines in good yields. The reactions of 3-phenylacetylquinoxalin-2(1*H*)-one **37g** with 3,4-diaminotoluene **5d**, or 4-nitro-1,2-DAB **5h**, produce a mixture of two isomers in almost equal amounts (Table 6.2) (Mamedov et al. 2008a; Saifina 2009), as evident from the ^{1}H NMR spectra of the crude products.

This is due to the fact that the probability of an initial attack of the amino group on the C(3) atom of the quinoxalin-2(1*H*)-one system and on the aroyl- or alkanoyl group during the rearrangement is approximately the same (Table 6.1) (Kalinin et al. 2000, 2007; Mamedov et al. 2004, 2008a, 2010a).

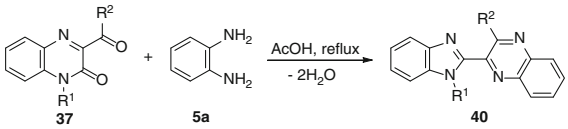
As can be seen from Table 6.1, it makes no difference for the reaction whether or not there is a substituent of quinoxalin-2(1*H*)-ones at position 1. The same process is successful with *N*-alkylated derivatives of quinoxalin-2(1*H*)-ones, producing *N*-alkylated derivatives of benzimidazole as well. All these reactions proceed with the formation of 2-(benzimidazol-2-yl)quinoxalines almost in quantitative yields.

The reaction proceeds with the compounds with two quinoxalin-2(1*H*)-one fragments in their composition, as well and there is no difference, what kind of spacer connects these two fragments. In all cases the reactions proceed smoothly with the formation of benzimidazole-monopodands with the terminal quinoxaline fragments (Table 6.3) (Mamedov et al. 2006; Kalinin et al. 2007; Isaykina 2007).



Scheme 6.29 Rearrangement of 3-benzoylquinoxalin-2(1*H*)-one

Table 6.1 Acid-catalyzed rearrangement of quinoxalin-2-ones when exposed to 1,2-DAB **5a**



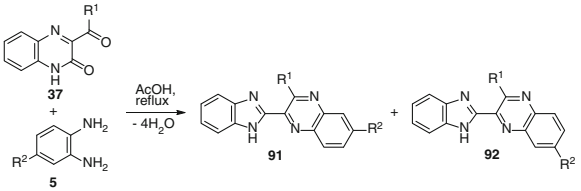
Entry	Substrate	R^1	R^2	Product	Yield (%)	Reference
1	**37b**	H	C_6H_4F-4	**40b**	94	Mamedov et al. (2010a)
2	**37c**	H	C_6H_4Cl-4	**40c**	97	
3	**37d**	H	C_6H_4Br-4	**40d**	95	
4	**37e**	H	C_6H_4I-4	**40e**	93	
5	**37f**	H	$C_6H_4NO_2$-4	**40f**	92	
6	**37g**	H	CH_2Ph	**40g**	81	Mamedov et al. (2008a)
7	**37h**	H	CH_2CH_2Ph	**40h**	87	
8	**37i**	H	*n*-Pr	**40i**	82	
9	**37j**	H	Me	**40j**	72	Kalinin et al. (2007)
10	**37k**	Et	Me	**40k**	99	
11	**37l**	Me	Ph	**40l**	81	Mamedov et al. (2004)
12	**37m**	Et	Ph	**40m**	79	
13	**37n**	*n*-Pr	Ph	**40n**	87	
14	**37o**	*n*-Bu	Ph	**40o**	87	
15	**37p**	*n*-Pent	Ph	**40p**	86	
16	**37q**	CH_2Ph	Ph	**40q**	56	
17	**37r**	COMe	Ph	**40r**	81	

While the reaction of 1,5-*bis*(3-benzoyquinoxalin-2(1*H*)-on-1-yl)pentane **93f** with the 3,4-diaminotoluene **5d** was carried out under the same conditions the formation of a single product mainly the benzimidazole-monopodand **94f** with the terminal quinoxaline systems in a 77 % yield actually occurs (Scheme 6.30) (Mamedov et al. 2006).

These systems contain methyl groups at C(6) and C(7′), and not at the C(6), C (6′) and C(7), C(7′) positions. This indicates that the probability of an initial attack on the amino group on the C(3) atom or on the benzoyl group is roughly the same. Otherwise, the formation of three products of rearrangement could be observed in approximately equal amounts.

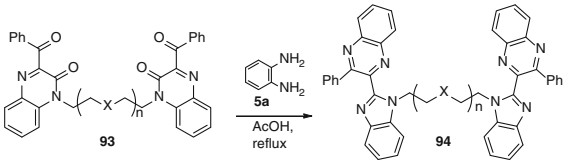
The use of pyrido[2,3-*b*]pyrazin-3(4*H*)-ones **95** instead of quinoxalinones **37** in the rearrangement considered here makes it possible to synthesize aza-analogues of benzimidazoles–1*H*-imidazo[4,5-*b*]pyridines **96** which are not easily accessible by classical Phillips-Ladenburg (Ladenburg 1875; Phillips 1928a, b; Ogg and Bergstrom 1931; Preston 1974; Hudkins 1995; White et al. 2000) and Weidenhagen (1936) (Tollari et al. 1994; White et al. 2000; Beaulieu et al. 2003; Kim et al. 2002;

Table 6.2 Acid-catalyzed rearrangement of quinoxalin-2-ones when exposed to 3,4-diaminotoluene **5d** and 4-nitro-1,2-DAB **5h**



Entry	**37**	R^1	**5**	R^2	Products (yield)	Reference
1	**37a**	Ph	**5d**	Me	**91a** + **92a** (82 %)	Mamedov et al. (2004)
2	**37g**	CH_2Ph	**5d**	Me	**91b** + **92b** (34 %) (44 %)	Mamedov et al. (2008a)
3	**36a**	Ph	**5h**	NO_2	**91c** + **92c** (39 %) (44 %)	Mamedov et al. (2004)
4	**36b**	C_6H_4F-4	**5h**	NO_2	**91d** + **92d** (47 %) (38 %)	Mamedov et al. (2010a)
5	**36c**	C_6H_4Cl-4	**5h**	NO_2	**91e** + **92e** (42 %) (36 %)	
6	**36d**	C_6H_4Br-4	**5h**	NO_2	**91f** + **92f** (45 %) (43 %)	
7	**36e**	C_6H_4I-4	**5h**	NO_2	**91g** + **92g** (44 %) (45 %)	
9	**36g**	CH_2Ph	**5h**	NO_2	**91h** + **92h** (36 %) (49 %)	Mamedov et al. (2004)

Table 6.3 Preparation of the symmetric benzimidazole-monopodands



Entry	Substrate	*X*	*n*	Product	Yield (%)
1	**93a**	O	1	**94a**	80
2	**93b**	O	2	**94b**	75
3	**93c**	CH_2	1/3	**94c**	69
4	**93d**	CH_2	4/3	**94d**	72
5	**93e**	CH_2	8/3	**94e**	73

Scheme 6.30 Preparation of the nonsymmetric benzimidazole-monopodand

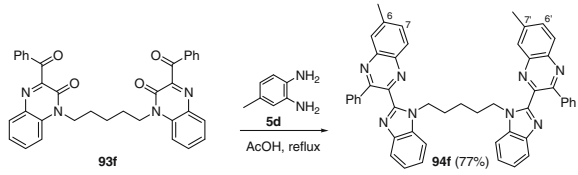
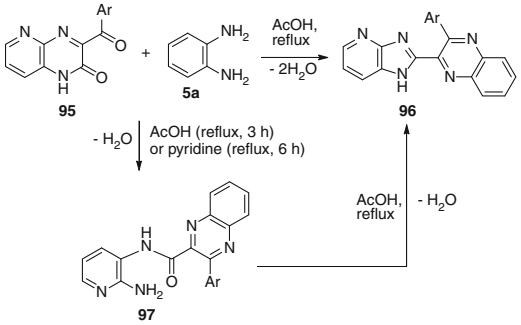


Table 6.4 Synthesis of 2-(1*H*-imidazo[4,5-*b*]pyridin-2-yl)-3-arylquinoxalines



Entry	Substrate	Ar	Product	Yield (%)
1	**95a**	Ph	**96a**	69
2	**95b**	C_6H_4F-4	**96b**	44
3	**95c**	C_6H_4Cl-4	**96c**	41
4	**95d**	C_6H_4Br-4	**96d**	43
5	**95a**	Ph	**97a**	64[a], 72[b]
6	**97a**	Ph	**96a**	84

[a]Obtained in refluxing pyridine
[b]Obtained in refluxing AcOH

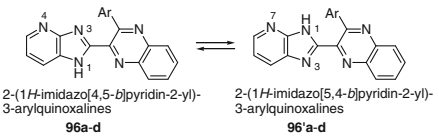


Fig. 6.4 Tautomerism in imidazopyridines

Elchaninov and Elchaninov 2014) reactions. The formation of 2-(1*H*-imidazo[4,5-*b*]pyridin-2-yl)-3-arylquinoxalines **96a–d** from pyrido[2,3-*b*]pyrazin-2(1*H*)-ones **95a–d** and 1,2-DAB **5a** proceeds in AcOH under reflux for 35–47 h. It should be noted, that carrying out the reaction with refluxed AcOH for 3 h leads to the formation of 2-amino-3-azaanylide quinoxaline 3-phenyl-2-carboxylic acids **97**. This has been illustrated by the reaction of 2-(1*H*-imidazo[4,5-*b*]pyridin-2-yl)-3-phenylquinoxaline **95a** and 1,2-DAB **5a** (Table 6.4) (Mamedov et al. 2010a).

Compounds **96a–d**, in contrast to the compounds **40a–d** with the benzimidazole system in the investigated solutions of DMSO-d_6 exist as a tautomeric mixture of **96a–d** ⇄ **96′a–d**, resulting in the dissymmetric 1*H*-imidazo[4,5-*b*]pyridine system (Fig. 6.4). Benzimidazoles as imidazoles with a ring *N*-hydrogen are subjected to tautomerism, which becomes evident in unsymmetrically substituted compounds (Joule and Mills 2010b). In the cases of imidazo[4,5-*b*]pyridines **96a–d** the dissymmetry was caused by the nitrogen atom of the pyridine ring.

6.4.2 *Synthesis of 2,3-*Bis*(benzimidazol-2-yl)quinoxalines*

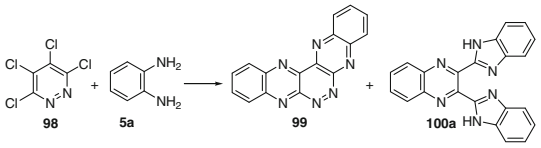
Obviously, it is not a simple task to obtain high results in the synthesis of heterocyclic systems with two directly connected benzimidazole fragments with the known methods [by Phillips-Ladenburg (Ladenburg 1875; Phillips 1928a, b; Preston 1974; Hudkins 1995; Grimmett 1997; White et al. 2000) and Weidenhagen (Weidenhagen 1936; Tollari et al. 1994; White et al. 2000; Kim et al. 2002; Beaulieu et al. 2003; Elchaninov and Elchaninov 2014) reactions]. At least twice as many labor-consuming classical methods of the synthesis of benzimidazoles are involved.

It should be pointed out that there is only one paper (Kanoktanaporn et al. 1980) in which the formation of 2,3-*bis*(benzimidazol-2-yl)quinoxaline **100a** as a by product in the reaction of tetrachloropyridazine **98** and 1,2-DAB **5a** in *N*-methylpyrroldone at 115 °C for 17 h is described (Scheme 6.31). The yield of the main product of this reaction 5,6,7,8,13,14-hexaazapentaphene **99** obtained as a free base after treatment of the corresponding hydrochloride with aqueous sodium hydroxide is 15 %. The yield of the by-product–2,3-*bis*(benzimidazol-2-yl)quinoxaline **100a** has not been given in this paper. Therefore this method cannot be used, as a preparative one for the synthesis of 2,3-*bis*(benzimidazol-2-yl)quinoxalines. The synthesis of other heterocyclic systems with two benzimidazole fragments cannot be used either.

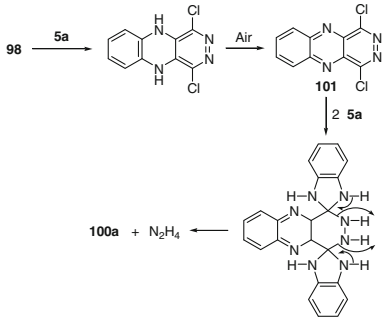
It was proposed that the quinoxaline residue of the product **100a** was formed by the initial nucleophilic attack on position 4 and 5 of tetrachloropyridazine **98** by 1,2-DAB, then the aerial oxidation, giving an intermediate 1,4-dichloropyridazino [4,5-*b*]quinoxaline **101** which might react with two more molecules of 1,2-DAB to give the pyridazine-ring-opened system **100a** (Scheme 6.32).

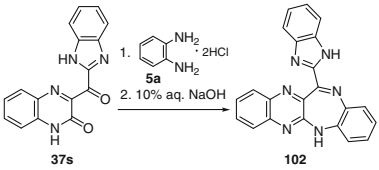
As can be seen from the above data (Sect. 6.4.1), the rearrangement proceeds very well with different aroyl- and alkanoyl- derivatives of quinoxalinones and as a

Scheme 6.31 The reaction of tetrachloropyridazine and 1,2-DAB

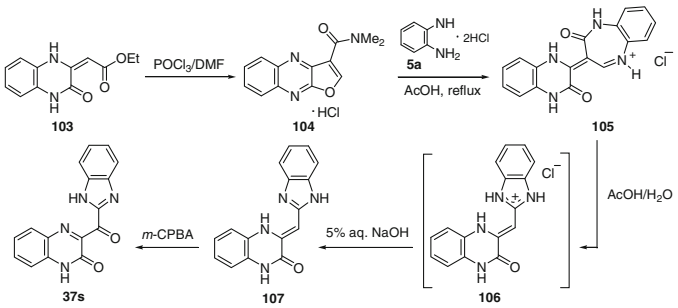


Scheme 6.32 Displacement of hydrazine hydrochloride from 1,4-dichloropyridazino [4,5-*b*]quinoxaline by 1,2-DAB





Scheme 6.33 The interaction of 3-benzimidazoylquinoxalin-2(1*H*)-one **37s** with 1,2-DAB dihydrochloride as described in literature (Kurasawa et al. 1985a)

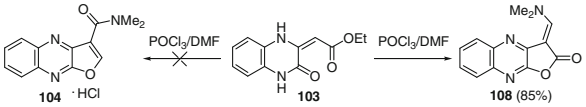


Scheme 6.34 The general scheme of the synthesis of 3-benzimidazoylquinoxalin-2(1*H*)-one **37s** starting with quinoxalin-2(1*H*)-one derivative **103** according to the references (Kurasawa et al. 1984, 1985a, b; Kurasawa and Takada 1980). The geometry of C=C double bond for quinoxaline derivative **107** is strongly supported by Gauge-Independent Atomic Orbital Calculations (Mamedov et al. 2014b)

result various benzimidazole derivatives are obtained. A further exploration of this strategy led them to examine how this rearrangement would proceed, if 3-heteroaroylquinoxalin-2(1*H*)-ones are used instead of alkanoyl- or aroylquinoxalin-2(1*H*)-ones. Among heteroaroyl groups the benzimidazoyl group was of primary interest for them since on the one hand, the successful course of the reactions of the 3-(benzimidazo-2-yl)quinoxalin-2(1*H*)-one (Kurasawa et al. 1985a) with 1,2-DABs opens up a new and effective way to obtain 2,3-*bis* (benzimidazol-2-yl)quinoxaline derivatives. The latter are inaccessible by any other known methods of constructing the benzimidazole system. On the other hand, this could prove whether the interaction of 3-(benzimidazo-2-yl)quinoxalin-2(1*H*)-one with 1,2-DAB dihydrochloride results in the benzodiazepine derivative, as previously cited in the literature (Kurasawa et al. 1985a) (Scheme 6.33).

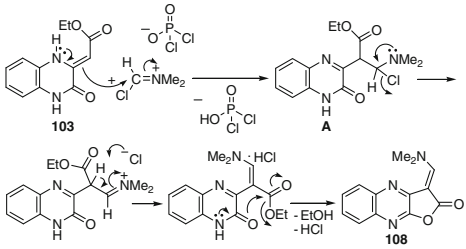
Kurasawa in his work (1985a) showed that the reaction of 3-benzimidazoylquinoxalinone **37 s** with 1,2-DAB dihydrochloride in boiling acetic acid resulted a benzodiazepine derivative **102** (Scheme 6.33).

Since this is contrary to the above findings on the reactions of aroylquinoxalin-2 (1*H*)-ones with 1,2-DAB (Kalinin et al. 2000, 2007; Mamedov et al. 2004, 2006, 2008a, 2010a; Hassner and Namboothiri 2012), it was decided to examine the results described in paper (Kurasawa et al. 1985a). With this intent it had been



Scheme 6.35 The reaction of 3-ethoxycarbonylmethylene-3,4-dihydroquinoxalin-2(1*H*)-one **103** with the Vilsmeier reagent

Scheme 6.36 A plausible mechanism for the formation of furo[2,3-*b*] quinoxalin-2-one derivative **108**



planned to synthesize 3-benzimidazoylquinoxalinone according to the following Scheme 6.34 developed by Kurasawa (Kurasawa et al. 1984, 1985a, b; Kurasawa and Takada 1980).

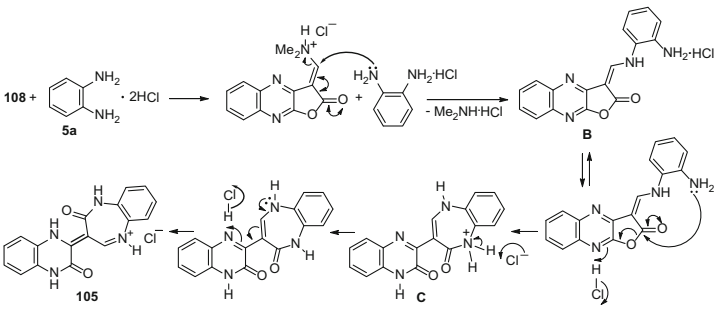
As can be seen from Scheme 6.34 at the very first stage compound **103** was allowed to react with the Vilsmeier reagent [DMF-$POCl_3$, 1:1], when heated on a water bath for 2 h, to give 3-(*N*,*N*-dimethylaminocarbonyl)furo[2,3-*b*]quinoxaline hydrochloride **104** (83 %) (Kurasawa and Takada 1980).

When carrying out this reaction, it was obtained a crystalline compound with almost the same spectral (IR, NMR) data, which are given in paper (Kurasawa and Takada 1980). However, the fact that the band at 1755 cm^{-1} in the IR spectrum that belongs to the C=O in the amide group (Kurasawa and Takada 1980) usually appears in the range of 1650–1690 cm^{-1} (Bellamy 1975) is appears more surprising.

After a detailed study of the structure of the reaction product, it was concluded that it is not the compound **104**, which is noncharacteristic for the dimethylcarbamoyl group but its isomer–1-*N*,*N*-dimethylaminomethylene-1,2-dihydrofuro [2,3-*b*]quinoxalin-2-one **108** (Scheme 6.35).

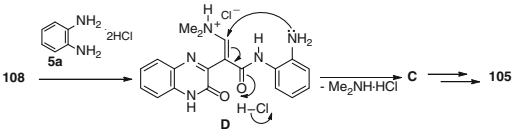
It is apparent that the formation of the furo[2,3-*b*]quinoxalin-2-one derivative **108** proceeds via the initial formation of compound **A** according to the first stage of the aliphatic Vilsmeier reaction, performed on the methylene group of the substituent at position 3 of quinoxalin-2(1*H*)-one **103**. The latter undergoes intramolecular cyclization with the subsequent elimination of EtOH and HCl results in the final product **108** (Scheme 6.36).

The next stage of the synthesis of 3-benzimidazoylquinoxalin-2(1*H*)-one **37s** according to Scheme 6.34 is the reaction of **104** with 1,2-DAB dihydrochloride in acetic acid which resulted in the ring transformation to afford 3-(3,4-dihydro-



Scheme 6.37 A possible mechanism of the formation of benzodiazepin-2(1*H*)-one derivative **105**

Scheme 6.38 A possible alternative mechanism for the formation of benzodiazepin-2(1*H*)-one derivative **105**



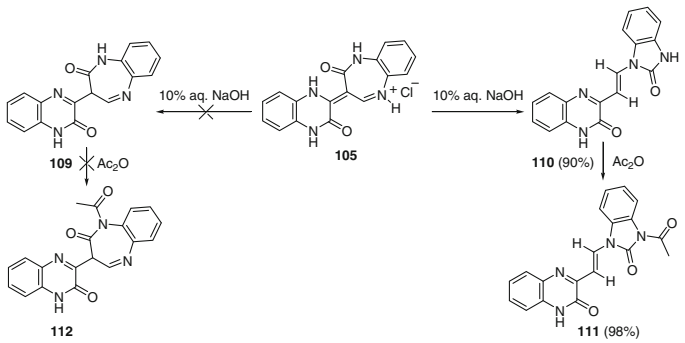
quinoxalin-2(1*H*)-on-3-yl)-1,2-dihydro-1,5-benzodiazepin-2(1*H*)-one hydrochloride **105** (Kurasawa et al. 1985b).

The reaction of **108** with 1,2-DAB dihydrochloride in the same conditions afforded a compound, which was identified by NMR spectroscopy as 3-(3,4-dihydroquinoxalin-2(1*H*)-on-3-yl)-1,2-dihydro-1,5-benzodiazepin-2(1*H*)-onium chloride **105** (Kurasawa et al. 1985b).

The formation of benzodiazepin-2(1*H*)-one derivative **105** can be due to the attack of the amino group of 1,2-DAB dihydrochloride on the activated carbon atom of the *N*,*N*-dimethylaminomethylene group of furo[2,3-*b*]quinoxalin-2-one derivative **108** by the HCl and results in the formation of intermediate **B**. The latter undergoes intramolecular ring closure and ring-opening processes, taking place by the addition of the nitrogen atom of the second amino group of 1,2-DAB to the carbonyl group of the furan ring, which results in the cleavage of the C–O bond to give the intermediate **C**. The 1,5-benzodiazepine system **C** is subsequently transformed into the final product **105** as shown below (Scheme 6.37).

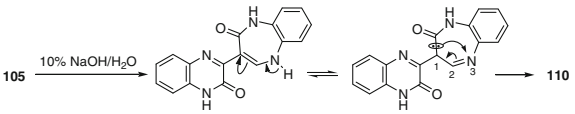
A possible mechanism for the formation of benzodiazepin-2(1*H*)-one derivative **105** (Scheme 6.38) can be alternatively written as follows; the amination with 1,2-DAB dihydrochloride would occur at the carbonyl carbon of **108**, forming the corresponding amide of 1,2-DAB and the subsequent intramolecular Michael addition of mono-*N*-acylated 1,2-DAB **D** to form the 1,5-benzodiazepine system **C**, which is subsequently transformed into the final product **105** (Scheme 6.38).

The spectral (^{1}H NMR, IR) data (Mamedov et al. 2014a, b) obtained for the product **105** differ from the data given for the product of the reaction of compound **104** with 1,2-DAB dihydrochloride in the paper (Kurasawa et al. 1985b). This difference prompted the authors (Mamedov et al. 2014a, b) to investigate the reaction of compound **105** with a 10 % NaOH solution in the EtOH at 90 °C and



Scheme 6.39 The treatment of benzodiazepin-2(1*H*)-one derivative **105** with 10 % aq. sodium hydroxide

Scheme 6.40 A plausible alternative mechanism for the formation of compound **110**



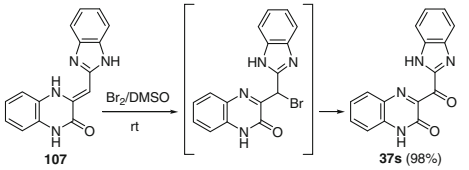
water-diluted acetic acid (1 volume part of AcOH, ~0.4 part H_2O) under reflux, as described for this compound in the papers (Kurasawa et al. 1985a, b). It was unexpected when the use of complex NMR methods proved that the reaction of compound **105** with a 10 % solution of NaOH in the EtOH solution proceeds with the formation of compound **110** in a 90 % yield, rather than the derivative of benzodiazepine **109** as shown in the paper (Scheme 6.39) (Kurasawa et al. 1985b).

It is reasonable to assume that the acylation of the reaction product **110** with acetic anhydride provides the formation of 3-[2-(3-acetylbenzimidazol-2-on-1-yl) vinyl]-1*H*-quinoxalin-2-one **111**, rather than the 3-(quinoxalin-2(1*H*)-on-3-yl)-1-acetyl-1,2-dihydro-3*H*-1,5-benzodiazepin-2-one **112** as shown in the paper (Kurasawa et al. 1985b) (Scheme 6.39).

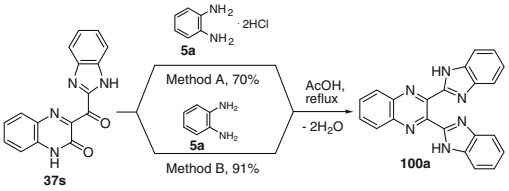
As to the structural hypothesis **109** (Kurasawa et al. 1985a, b), there can be several arguments not in its favor. First the **109** does not contain olefin fragments with the corresponding proton spin-system. Second, some of the calculated ^{13}C chemical shifts (CSs) deviate dramatically from those established experimentally. In particular, the C(3) (50 ppm) and the C(4) (146 ppm) which obviously disagree with experimental CSs (Mamedov et al. 2014a, b).

From the above results, the reaction mechanism from **105** to **110** might be formulated as a [1,3]-sigmatropic acyl shift analogous to that observed in related systems (Rossi et al. 1960; Von Barchet and Merz 1964; Kost et al. 1972; Achour et al. 1988; Howard et al. 1992; De Moliner and Hulme 2012; Eleftheriadis et al. 2013) (Scheme 6.40).

The mechanism of the formation of the **110** can be alternatively presented.



Scheme 6.41 The synthesis of 3-benzimidazoylquinoxalin-2(1*H*)-one **37s**



Scheme 6.42 The quinoxalinone-benzimidazole rearrangement in the reaction of 3-(benzimidazo-2-yl)quinoxalin-2(1*H*)-one **37s** with both 1,2-DAB dihydrochloride and 1,2-DAB

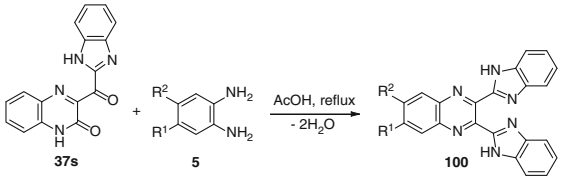
Heating at reflux of the benzodiazepine derivative **105** in the aqueous acetic acid solution affected ring transformation as has been shown in paper (Kurasawa et al. 1985a) to give **106**, the treatment of which with a 5 % sodium hydroxide yielded a free base **107** (Scheme 6.34). The final stage of the synthesis of 3-benzimidazoylquinoxalin-2(1*H*)-one **37s** according to Scheme 6.34 involves the oxidation of compound **107** with *m*-chloroperbenzoic acid (*m*-CPBA) (Kurasawa et al. 1985a). Since according to this method the yield of the desired product is approximately 40 %, was used the method of oxidation for the synthesis of 3-benzimidazoylquinoxalin-2(1*H*)-one **37s**, which has been recently developed for similar compounds. It includes the treatment of 3-(α-bromobenzyl)quinoxalin-2(1*H*)-ones with DMSO (Gorbunova and Mamedov 2006). The reaction of 3-(benzimidazol-2-yl)methylenequinoxalin-2(1*H*)-one **107** with an equimolar amount of bromine in DMSO at room temperature for 24 h results in ketone **37s** with a quantitative yield. According to the Kornblum oxidation (Kornblum et al. 1959; Kornblum and Frazier 1966; Chandrasekhar and Sridhar 2000; Bettadaiah et al. 2003) the formation of the latter can be represented as an oxo-dehydrohalo-bisubstitution (Smith 2013a) formed in situ 3-(α-bromomethylimidazol-2-yl)quinoxalin-2-(1*H*)-one (Scheme 6.41).

As can be expected the reaction of 3-(benzimidazo-2-yl)quinoxalin-2(1*H*)-one **37s** with 1,2-DAB dihydrochloride, proceeds with the formation of 2,3-*bis*-(1*H*-benzimidazol-2-yl)quinoxaline **100a** (Scheme 6.42), but not of the benzodiazepine derivative **102**, as described (Kurasawa et al. 1985a).

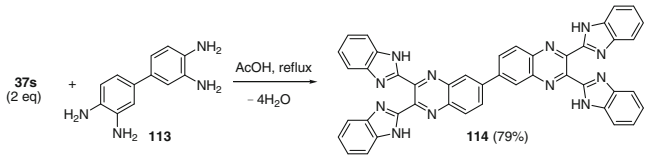
When 1,2-DAB is used instead of 1,2-DAB dihydrochloride in this reaction the yield of compound **100a** is almost quantitative.

Thus, the reactions of 3-benzimidazoylquinoxalin-2(1*H*)-one **37s** with both 1,2-DAB dihydrochloride and 1,2-DAB proceed according to the novel

Table 6.5 Scope of 1,2-DABs in 2,3-bis(benzimidazol-2-yl)quinoxaline formation



Entry	Substrate	R^1	R^2	Product	Yield (%)
1	**5c**	Me	Me	**100b**	90
2	**5d**	Me	H	**100c**	96
3	**5f**	Cl	H	**100d**	89
4	**5h**	NO_2	H	**100e**	83
5	**5l**	CO_2H	H	**100f**	76
6	**5m**	COPh	H	**100g**	80

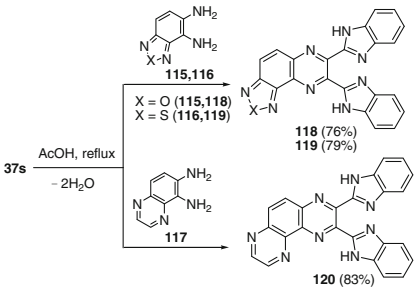


Scheme 6.43 The formation of 2,2′,3,3′-tetra(benzimidazol-2-yl)-6,6′-biquinoxaline

quinoxalinone-benzimidazole rearrangement (Mamedov and Murtazina 2011; Hassner and Namboothiri 2012). The formation of 2,3-bis(1*H*-benzimidazol-2-yl) quinoxaline **100a** and not the formation of the benzodiazepine derivative **102**, occurs, as has been described in the literature. The reactions of the synthesis of 3-benzimidazoylquinoxalin-2(1*H*)-one **37s** starting from 3-ethoxycarbonylmethylene-3,4-dihydroquinoxalin-2(1*H*)-one through the 3-(3,4-dihydroquinoxalin-2(1*H*)-on-3-yl)-1,2-dihydro-1,5-benzodiazepin-2(1*H*)-one hydrochloride **105** and 3-(benzimidazol-2-yl)methylenequinoxalin-2(1*H*)-one **107** have also been reexamined and the published results (Kurasawa and Takada 1980; Kurasawa et al. 1984, 1985a, b) have been appropriately amended. A simple and efficient one-pot method for the synthesis of 3-benzimidazoylquinoxalin-2(1*H*)-one **37s** directly from 3-(benzimidazol-2-yl)methylenequinoxalin-2(1*H*)-one **107** has been described.

3-(Benzimidazo-2-yl)quinoxalin-2(1*H*)-one **37 s** reacted not only with 1,2-DAB **5a** but also with its substituted analogues **5c**, **d**, **e**, **h**, **l**, **m** in AcOH at reflux. The formation of 2,3-bis(benzimidazol-2-yl)quinoxalines **100b–g** was observed in excellent 76–96 % isolated yields (Table 6.5) (Mamedov et al. 2013).

The scope of the methodology, was studied first with respect to the 3,3′-diaminobenzidine **113** (Scheme 6.43). As can be seen, this chemistry is not limited to mono- and disubstituted systems, a compound with two 1,2-diaminobenzene fragments is also an acceptable substrate (Mamedov et al. 2013).



Scheme 6.44 Scope of condensed 1,2-DABs in condensed 2,3-di (benzimidazol-2-yl) quinoxaline formation

The scope of this chemistry was also investigated with respect to the condensed 1,2-DABs. The 3-(benzimidazo-2-yl)quinoxalin-2(1*H*)-one **37s** was allowed to react with benzo[c]furane-4,5-diamine **115**, benzo[*c*]thiene-4,5-diamine **116** and quinoxaline-5,6-diamine **117** in AcOH at reflux (Scheme 6.44) (Mamedov et al. 2013). The isolated yields proved high enough as well.

Thus, the results of the reaction of 3-(benzimidazo-2-yl)quinoxalin-2(1*H*)-one **37s** with a variety of 1,4-di-*N*-nucleophiles confirm the hypothesis, which has been proposed earlier (Scheme 6.16) (Mamedov et al. 2010b, 2011a).

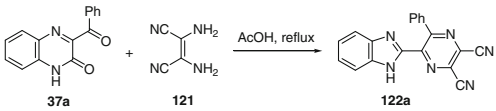
In this way, a simple, mild, robust, and high yielding one-pot protocol was devised to produce quinoxalines and tethered quinoxaline-benzimidazoles. The products have the potential to be further decorated and constrained using additional functional groups. Moreover, the generic nature and simplicity of the protocol renders it highly attractive as a valuable addition to the repertoire of synthetic transformations used by the organic and medicinal chemists respectively. Considering the well documented medicinal utility of benzimidazoles and quinoxalines, these tethered combinations of the two scaffolds afford new opportunities to probe their biological activity.

6.4.3 Synthesis of 2-(Pyrazin-2-yl)benzimidazoles

Further exploration of the above strategy with the use of diaminomaleonitrile instead of 1,2-DABs has led to the development of a novel, simple method for the synthesis of 2-benzimidazolylpyrazines. Here the results of study on a novel rearrangement of 3-aroyl- and alkanoylquinoxalin-2(1*H*)-ones and 2,3-diaminomaleonitrile as a *N*-nucleophile under the acid catalysis condition are presented (Mamedov et al. 2012).

Regardless of the molar ratio of the reagents (1:1, 1:1.1, 1:2; **37a**:**121**) and reaction time (3, 9 or 17 h) the reaction of 3-benzoylquinoxalin-2(1*H*)-one (3-BQ) **37a** with 2,3-diaminomaleonitrile **121** proceeded in the same way with the formation of ~45 % yield of the rearrangement product **122a** (Scheme 6.45), whereas 50 % of 3-benzoylquinoxalin-2(1*H*)-one **37a** reverted. Diaminomaleonitrile **121** apparently undergoes polymerization. Adding a second equivalent of

Scheme 6.45 Acid-catalyzed rearrangement

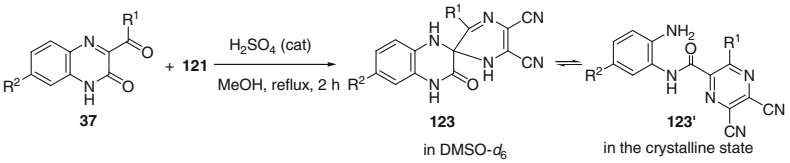


diaminomaleonitrile **121** to the reaction mixture obtained after boiling the equimolar ratio of reagents in acetic acid for 5 h did not lead to an increased yield of the desired product. Neither did the boiling for an additional 5 h.

In order to improve the yield of the rearrangement product there were used the previously proposed hypothesis (Scheme 6.16) (Mamedov et al. 2010b, 2011a).

In accordance with this hypothesis there appeared the problem of the synthesis of the spiro[pyrazine-2,2′-quinoxalin]-3′(4′*H*)-one derivative. For this purpose we installed the necessary pyrazine ring system at position 2 of quinoxalin-2(1*H*)-one **37a** via the modified Körner and Hinsberg (1887) (Murthy et al. 2010) reaction (the synthesis of quinoxalines by condensation of α-dicarbonyl compounds with 1,2-DAB). This was achieved by the reaction of **37a** with diaminomaleonitrile **121** in a boiling solution of MeOH in the presence of a catalytic amount of H_2SO_4. In this reaction we considered the 3-BQ **37a** to be a heteroanalogue of an α-dicarbonyl compound. The reaction proceeded smoothly for 2 h to give the desired spiro-compound, 5,6-dicyano-3R-1*H*,1′*H*-spiro[pyrazine-2,2′-quinoxalin]-3′(4′*H*)-one **123a** in 96 % yield (Table 6.6, entry 1). The optimum molar ratio of reagents **37a**:**121** was 1.0:1.1. Under these conditions other 3-aroyl- (**37a–e**, **t**, **u**) and 3-alkanoyl- (**37g**, **i**) derivatives of quinoxalin-2(1*H*)-ones behaved similarly resulting in high (75–96 %) yields of the corresponding spiro-derivatives on

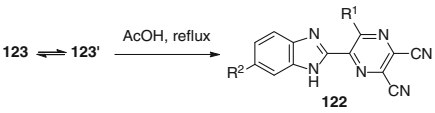
Table 6.6 Synthesis of 5,6-dicyano-3*R*-1*H*,1′*H*-spiro[pyrazine-2,2′quinoxalin]-3′(4′*H*)-ones



Entry	Substrate	R^1	R^2	Product	Yield (%)
1	**37a**	Ph	H	**123a**	96, 74[a], 91[b]
2	**37b**	C_6H_4F-4	H	**123b**	92, 85[a], 88[b]
3	**37c**	C_6H_4Cl-4	H	**123c**	93, 82[a]
4	**37d**	C_6H_4Br-4	H	**123d**	93, 77[a]
5	**37e**	C_6H_4I-4	H	**123e**	95, 77[a]
6	**37t**	Ph	COPh	**123f**	95, 61[a]
7	**37u**	Ph	CO_2H	**123g**	89, 64[a]
8	**37g**	CH_2Ph	H	**123h**	95, 60[a]
9	**37j**	Me	H	**123i**	75, 61[a]

[a]*p*-TsOH was used instead of H_2SO_4
[b]HCl was used instead of H_2SO_4

Table 6.7 Acid-catalyzed rearrangement of 5,6-dicyano-3*R*-1*H*,1′*H*-spiro[pyrazine-2,2′-quinoxalin]-3′(4′*H*)-ones



Entry	R^1	R^2	Time	Product	Yield (%)
1	Ph	H	10 min	**122a**	90
2	C_6H_4F-4	H	10 min	**122b**	90
3	C_6H_4Cl-4	H	10 min	**122c**	91
4	C_6H_4Br-4	H	10 min	**122d**	89
5	C_6H_4I-4	H	10 min	**122e**	92
6	Ph	COPh	3 h	**122f**	89
7	Ph	CO_2H	3 h	**122g**	85
8	CH_2Ph	H	10 min	**122h**	92
9	Me	H	10 min	**122i**	93

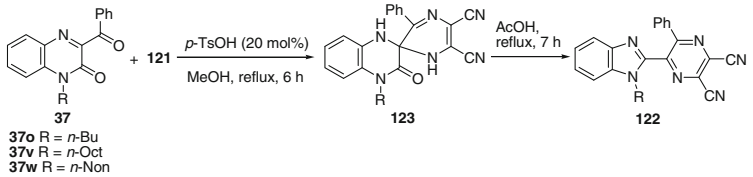
reaction with diaminomaleonitrile **121** (Table 6.6). These examples of the reactions of **37a**, **d** with **121** showed that increasing the reaction time up to 10 h resulted in a mixture of the products of rearrangement of **122a**, **d** and spiro-derivatives of quinoxalinones **123a**, **d** in a ratio of ~1:3 (yield 89 %), and up to 20 h in a ratio of ~1:1 (yield 97 %). When carrying out the reactions of quinoxalines **37a–e**, **g**, **j**, **t**, **u** with diaminomaleonitrile **121** for 6 h in the presence of *p*-TsOH (20 mol%) as a catalyst the formation of spiro-compounds **123a–i** occurred in yields of 60–85 % (Table 6.6). The reactions of quinoxalin-2(1*H*)-ones **37a**, **b** with **121** show that in the presence of catalytic amounts of HCl, spiro-compounds **123a**, **b** are formed in 2 h and the yields of products were 91 and 88 %, respectively (entries 1 and 2).

Spiro-compounds **123a–e**, **h**, **i** without substituents on the benzene ring of the quinoxaline system were quantitatively transformed into the desired 2-(pyrazin-2-yl) benzimidazole **122a–e**, **h**, **i** in boiling AcOH in 10 min (Table 6.2, entries 1–5, 8, 9). The substituted spiro-derivatives of quinoxalin-2(1*H*)-ones **123f**, **g** underwent the rearrangement only after 3 h in boiling AcOH (Table 6.7, entries 6, 7).

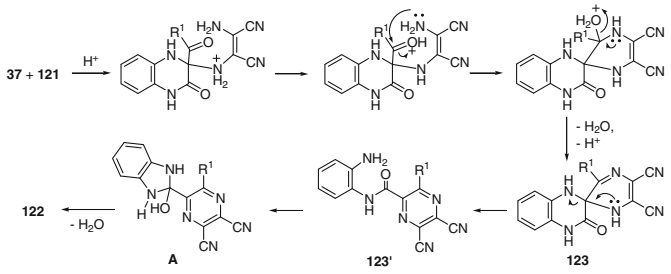
The formation of spiro-compounds also proceeded with the *N*-alkylated derivatives of quinoxalin-2(1*H*)-ones **37o**, **v**, **w** to give *N*-alkylated spiro [pyrazine-2,2′-quinoxalin]-3′(4′*H*)-ones **123j–l** (Table 6.8). *p*-TsOH was more suitable as the catalyst for these cases. It should be pointed out that the rearrangement of *N*-alkylated spiro-compounds **123j–l** occurred more slowly than with nonalkylated spiro-compounds **123a–i**. Thus, boiling the spiro-compounds **123j–l** for 5 min resulted in the formation of the product of rearrangement in a ~25 % yield, 30 min: ~50 %, 3 h: ~75 %, 7 h: ~100 %.

It is worthy of note that the products of the reaction of 3-aroyl(alkanoyl) quinoxalin-2(1*H*)-ones **37a–e**, **g**, **i**, **t**, **u** and *N*-alkyl-3-BQs **37o**, **v**, **w** with diaminomaleonitrile **121** in DMSO-d_6 exist solely in spiro-cyclic-forms **123a–l**, whereas in the crystalline state they exist only as open chain forms **123′a–l** (Mamedov et al. 2012).

Table 6.8 The synthesis of 4-alkyl 5,6-dicyano-1*H*,1′*H*-spiro[pyrazine-2,2′-quinoxalin]-3′-ones and 1-alkyl-2-(pyrazin-2-yl)benzimidazoles



Entry	R	Product	Yield (%)
1	*n*-Bu	**123j**	95
2	*n*-Oct	**123k**	94
3	*n*-Non	**123l**	97
4	*n*-Bu	**122j**	58
5	*n*-Oct	**122k**	60
6	*n*-Non	**122l**	60



Scheme 6.46 A plausible mechanism for the formation of 2-(pyrazin-2-yl)benzimidazoles **122**

On the basis of the known chemistry of quinoxalinones (Cheeseman and Cookson 1979), diaminomaleonitrile (Faust and Weber 1997; Gao et al. 2006; Kubota et al. 2009), and the above data, it is reasonable to assume that the formation of 2-(pyrazin-2-yl)benzimidazoles **122** involves addition of the amino group of diaminomaleonitrile **121** at the C(3) atom of quinoxalin-2(1*H*)-one **37** as the first step. The next step involves nucleophilic attack of the second amino group of **121** on the benzoyl carbonyl group to form the spiro-quinoxaline derivative **123**. Rearrangement of the spiro-quinoxalinone **123** is then assumed to occur according to Scheme 6.46, which proceeds via cascade reactions involving: (a) acid-catalyzed ring-opening with cleavage of the C(3)–N(4) bond in the spiro-compound **123** with the formation of an intermediate quinoxaline derivative **123′**, (b) intramolecular nucleophilic attack by the amino group on the carbonyl group with the formation of intermediate hydroxy-derivative **A**, and (c) elimination of water leading to the final product **122** (Scheme 6.46).

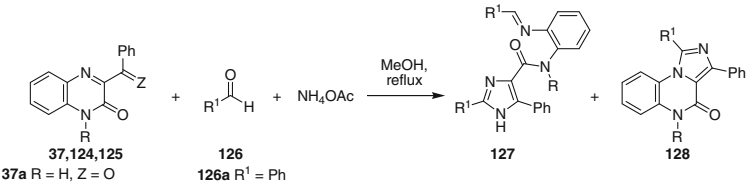
An efficient and versatile metal-free method for the preparation of a series of 2-(pyrazin-2-yl)benzimidazoles has been developed. This was accomplished by the

novel rearrangement of 3R-5,6-dicyano-1*H*,1′*H*-spiro[pyrazine-2,2′-quinoxalin]-3′(4′*H*)-ones easily obtained from 3-aroyl- and 3-alkanoylquinoxalin-2(1*H*)-ones on exposure to diaminomaleonitrile. The key advantages are the simplicity of the operation, high yields, easy availability of 3-aroyl- and alkanoylquinoxalin-2(1*H*)-ones, as well as the simple workup and purification of the products. The reaction is readily applicable to large-scale synthesis.

6.4.4 Synthesis of 2-(Imidazol-4-yl)benzimidazoles

In continuation of the efforts to develop quinoxalin-2(1*H*)-one (Mamedov et al. 2008a, b, 2009a, 2010a, c) based synthetic methodologies, a simple, mild, and expeditious synthesis of 2,4,5-trisubstituted imidazoles in high yields using 3-aroylquinoxalin-2(1*H*)-ones as hetero analogues of α-diketones has been developed (Mamedov et al. 2011b, c). Initially, 3-BQ **37a** (1 mmol), benzaldehyde **126a** (1 mmol) and ammonium acetate (2 mmol) in boiling methanol for 7 h, was condensed which led to a very poor yield (5 %) of a mixture of 2,4,5-trisubstituted

Table 6.9 Condensation of 3-benzoylquinoxalin-2(1*H*)-one and its derivatives, arylaldehydes and ammonium acetate under various condition



37,124,125
37a R = H, Z = O
37o R = *n*-Bu, Z = O
124 R = H, Z = NC_6H_4Me-2
125 R = H, Z = NC_6H_4Me-4

126
126a R^1 = Ph
126b R^1 = C_6H_4Br-4
126c R^1 = $C_6H_4NO_2$-4

127

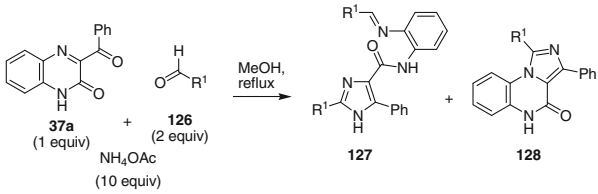
128

Entry	Substrates		Ratio**1/2/NH$_4$OAc**	Time (h)	Products	Ratio**127/128**[a]	Total yield (%)
							127 + 128
1	**37a**	**126a**	1/1/2	9	**127a + 128a**	2/1	5 (7)[b]
2	**37a**	**126a**	1/1/10	9	**127a + 128a**	1.8/1	30
3	**37a**	**126a**	1/2/10	7	**127a + 128a**	2/1	79 (79)[c]
4	**37a**	**126a**	1/3/10	7	**127a + 128a**	2/1	52
5	**37a**	**126b**	1/2/10	7	**127b + 128b**	1.4/1	83
6	**37a**	**126c**	1/2/10	7	**127c + 128c**	2.7/1	70
7	**37o**	**126a**	1/2/10	7	**127d + 128d**[d]	Trace/1	52
8	**124**	**126a**	1/2/10	7	**127a + 128a**	1/1.2	61
9	**125**	**126a**	1/2/10	7	**127a + 128a**	4/1	64
10	**125**	**126b**	1/2/10	7	**127b + 128b**	2/1	59

[a]The ratio of compounds **127** and **128** was determined by ^{1}H NMR spectroscopy
[b]Isolated yield after reflux for 15 h
[c]Isolated yield when the reaction was carried out in the presence of L-proline
[d]Isolated yield of **128d** = 42 %

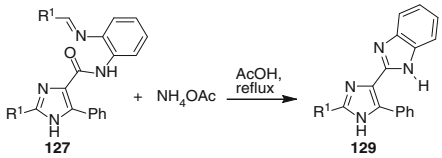
imidazole **127a** and imidazo[1,5-*a*]quinoxalin-4(5*H*)-one **128a** in the ratio 2:1 (Table 6.9, entry 1). To enhance the yield of the desired product the reaction time was increased to 15 h but no appreciable increase in the product yield was observed (Table 6.9). There remained a large amount of the unreacted 3-BQ **37a** and benzaldehyde **126a** in the reaction mixture. It was considered worthwhile to carry out the reaction using various ratios of 3-BQ **37a** and benzaldehyde **126a** and ammonium acetate starting with 1:1:10 (entry 2), 1:2:10, and 1:3:10. A maximum yield (79 %) of a mixture of imidazole **127a** and imidazo[1,5-*a*]quinoxalin-4(5*H*)-one **128a** was obtained with a 1:2:10 ratio of the reagents (entry 3). A further increase in the amount of benzaldehyde **126a** (ratio of 1:3:10) did not affect the yield, but slightly slowed the reaction which did not depend on the reaction time. Unreacted benzaldehyde **126a** remained in the reaction mixture (entry 4). When the reaction was carried out in the presence of the organocatalyst *L*-proline, no enhancement in the yield of the desired product was observed. When 3-{α-[2-(or 4)-methylphenylimino]benzylidene}-quinoxalin-2(1*H*)-ones **124**, **125** were used instead of **37a**, the total yields of the mixture remained approximately the same, but in the case of quinoxalin-2(1*H*)-ones **125** the ratio of products **127a** and **128a** increased in favor of the former and reached 4:1 (entry 9). When the reaction was carried out with 1-(*n*-butyl)-3-benzoylquinoxalin-2-one **37o** the formation of 1,3-diphenyl-5-butylimidazo[1,5-*a*]quinoxalin-4(5*H*)-one **128d** was observed as almost the sole product (entry 7).

Table 6.10 3-Aroylquinoxalin-2(1*H*)-one derivatives as hetero analogues of α-diketones in the synthesis of functionalized imidazoles



Entry	Substrate	R^1	Products (yield)
1	**126a**	Ph	**127a** + **128a** (49 %) (26 %)
2	**126b**	C_6H_4Br-4	**127b** + **128b** (47 %) (33 %)
3	**126c**	$C_6H_4NO_2$-4	**127c** + **128c** (47 %) (17 %)
4	**126d**	C_6H_4F-4	**127e** + **128e** (45 %) (26 %)
5	**126e**	C_6H_4Cl-4	**127f** + **128f** (40 %) (28 %)
6	**126f**	C_6H_4I-4	**127g** + **128g** (44 %) (29 %)
7	**126g**	Py-3	**127h** + **128h** (38 %) (42 %)

Table 6.11 An efficient method for synthesizing 2-(imidazol-4-yl)benzimidazoles **129a–d**



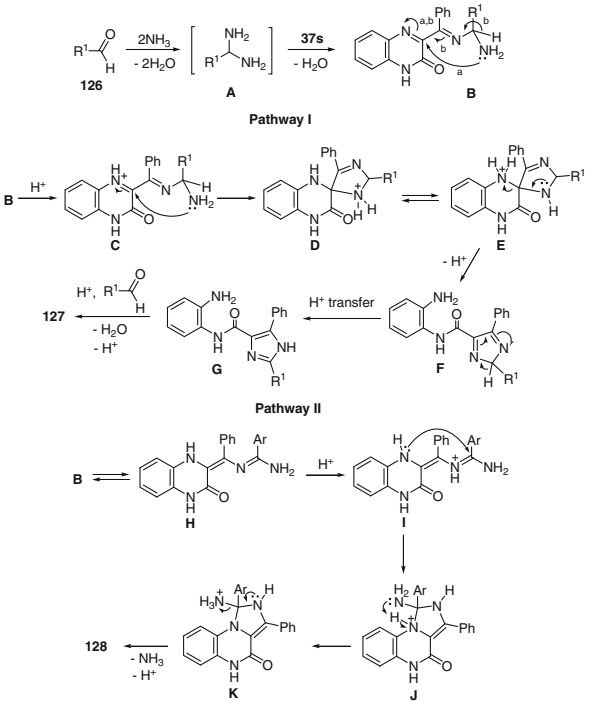
Entry	Substrate	R^1	Product	Yield (%)
1	**127a**	Ph	**129a**	94
2	**127c**	$C_6H_4NO_2$-4	**129b**	99
3	**127e**	C_6H_4F-4	**129c**	98
4	**127h**	Py-3	**129d**	95

To determine the scope and generality of this reaction, various substituted aldehydes and 3-pyridinecarboxaldehyde has been utilized. The desired products are obtained and the results are summarized in Table 6.10.

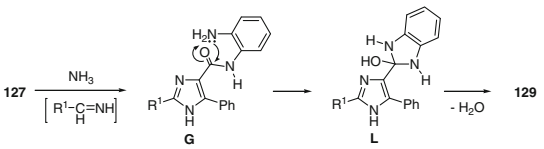
The presence of the *o*-iminoanilide substituent at position 4 of imidazoles **127** makes it possible to use them in further syntheses. Based on the four imidazole derivatives **127a**, **c**, **e**, **h,** it was shown that the reaction of these compounds with ammonium acetate in acetic acid proceeds with the formation of 2-(imidazol-4-yl) benzimidazoles **129a–d** in almost quantitative yields (Table 6.11).

A plausible mechanism for the synthesis of imidazoles, imidazo[1,5-*a*] quinoxalin-4(5*H*)-ones, and benzimidazoles has been proposed (Scheme 6.47). The formation of the diamine intermediate **A** takes place during the initial stage of the reaction. Intermediate **A** condenses with the 3-benzoylquinoxalin-2(1*H*)-one **37s** followed by dehydration to afford the imino intermediate **B**, which is transformed in two different ways (*Pathway I* and *Pathway II*). *Pathway I* proceeds by cascade reactions involving: (a) acid-catalyzed ring closure of intermediate **C** with the formation of spiro-compound **D**, (b) acid-catalyzed ring-opening of spiro-compound **E** with the formation of the imidazole derivative **F**, which is rearranged into the imidazole derivative **G** via a [1,5] hydrogen shift, and (c) reaction of the latter with the aldehyde to form compound **127**. *Pathway II* involves the tautomerism of intermediate **B** with the formation of compound **H**, which under acid catalysis undergoes intramolecular cyclization to give **I**. The final product **128** is formed following the elimination of ammonia through intermediates **J** and **K**.

It is apparent that the formation of 2-(imidazol-4-yl)benzimidazoles **129a–d** involves the ammonolysis of imidazoles **127a**, **c**, **d**, **g** to form the corresponding *o*-aminoanilide derivative **G** as the first step. The next step involves an intramolecular nucleophilic attack by the amino group on the carbonyl group with the formation of



Scheme 6.47 A plausible mechanism for the formation of imidazoles. *Pathway I*–acid catalysis through ring-closure and ring-opening processes. *Pathway II*–via a novel acid catalysis imidazoannulation of quinoxalin-2(1*H*)-ones



Scheme 6.48 A possible mechanism for the formation of 2-(imidazol-4-yl)benzimidazoles **129**

the intermediate hydroxy-derivative **L**, and then the elimination of water. This leads to the formation of the final product **129** (Scheme 6.48).

This was accomplished by the novel ring-opening of 3-aroylquinoxalin-2(1*H*)-ones on exposure to diaminoarylmethanes intermediately generated from arylaldehydes and ammonium acetate. The introduction of the *o*-iminoanilide fragment at position 4 of the imidazole derivatives with the help of this method makes it possible to synthesize 2-(imidazol-4-yl)benzimidazoles. The simplicity of this method, high yields, easy workup, and purification of compounds by crystallization are the key advantages.

6.5 Synthesis of 2-(3-Arylindolizin-2-yl)benzimidazole via the Rearrangement (Use of 3-α-Chlorobenzyl- and α-Chloroalkylquinoxalin-2(1*H*)-ones as Analogues of α-Haloketones)

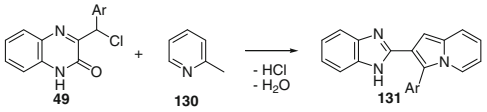
One of the common reactions of α-haloketones in the chemistry of heterocycles is the Chichibabin reaction, that is, the synthesis of indolizines by interaction of α-picoline with α-haloketones. This was carried out in a series of reactions according to Chichibabin. Thus, the reaction of quinoxalin-2-one **49** (the schematical presentation of the 3-α-chlorobenzyl- and α-chloroalkylquinoxalin-2(1*H*)-ones as analogues of α-haloketones has been shown in Sect. 6.2.3(E) (see Fig. 6.3, structure **49**)) with α-picoline **130** at reflux results in high yields of the corresponding 2-(indolizinyl)benzimidazoles **131** (Table 6.12). As is evident from the structure of compounds **131**, the C(2)–C(3)–C(Cl)Ar and N=C–Me fragments of quinoxaline **49** and α-picoline **130** are involved in constructing the two new heterocyclic rings (Mamedov et al. 2008b, 2009b; Saifina 2009).

Initially, a complete dissolution of compounds **49** is observed in refluxing the α-picoline solution, after that there rapidly occurs an abundant precipitation of crystals which gradually dissolve during the course of the reaction. The yield of crystalline products with a precise melting point, are obtained, for example, after refluxing quinoxalin-2(1*H*)-one **49c** in α-picoline **130** for 1 h, and the yield is 41 % (Table 6.13).

It should be noted that spiro-compound **132** is quantitatively transformed into 2-(3-arylindolizin-2-yl)benzimidazole **131** not only in boiling α-picoline, but also in acetic acid (Scheme 6.49).

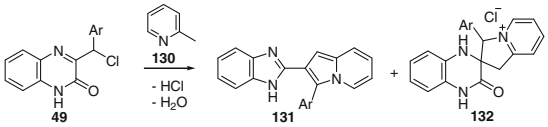
A first-stage product resulting from the nucleophilic displacement of the Cl atom by the pyridine N atom of α-picoline under milder reaction conditions is isolated and characterized and is then required for the formation of a spiro-compound or its

Table 6.12 Synthesis of benzimidazoles from quinoxalinones and α-picoline via rearrangement

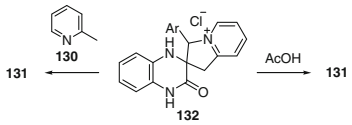


Entry	Substrate	Ar	Product	Yield (%)
1	**49a**	$C_6H_4NO_2$-4	**131a**	72
2	**49b**	Ph	**131b**	78
3	**49c**	C_6H_3-di-Cl-2,4	**131c**	76
4	**49d**	C_6H_3-di-Cl-3,5	**131d**	65
5	**49e**	CH_2Ph	**131e**	70

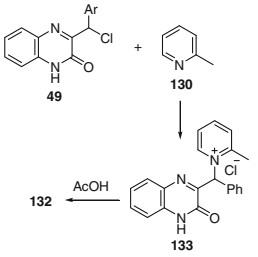
Table 6.13 Isolated and characterized spiro-compounds, formed after the reaction mixture is boiled for an hour, are presented



Entry	Substrate	Ar	Product	Yield (%)
1	**49a**	$C_6H_4NO_2$-4	**132a**	10
2	**49b**	Ph	**132b**	37
3	**49c**	C_6H_3-di-Cl-2,4	**132c**	41
4	**49d**	C_6H_3-di-Cl-3,5	**132d**	16



Scheme 6.49 The rearrangement of spiro-quinoxalinones **132**



Scheme 6.50 The synthesis and rearrangement of 2-methyl-1-[(3-oxo-3,4-dihydroquinoxalin-2-yl)(phenyl)methyl]pyridinium chloride **133**

rearrangement into a benzimidazole derivative. For instance, when 3-(α-chlorobenzyl)quinoxalin-2(1*H*)-one **49** was stirred in α-picoline **130** at 50 °C for 3 h (Scheme 6.50), the crystals formed were assigned the structure **133** (Saifina 2009).

The formation of a rearrangement product can be represented by Scheme 6.51. According to this scheme, the initial step involves the nucleophilic displacement of the Cl atom by the pyridine N atom, which is followed by a cascade transformation. The latter involves: (a) dehydrochlorination with the abstraction of a methyl H atom of α-picoline, (b) intramolecular nucleophilic addition of the methylidene C atom of the α-picoline fragment to the azomethine C atom of the quinoxaline system

Scheme 6.51 Proposed mechanism of the rearrangement

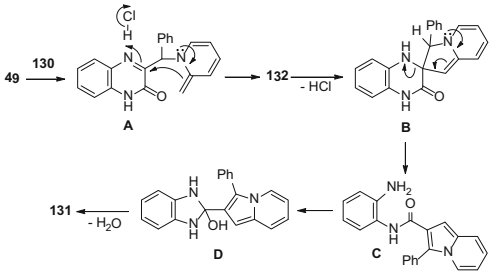
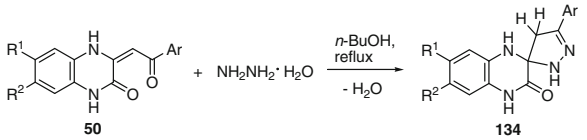


Table 6.14 Synthesis of 3′-aryl-1,2,3,4,4′,5′-hexahydro[quinoxalin-2,5′-pyrazol]-3-ones



Entry	Substrate	R^1	R^2	Ar	Product	Yield (%)
1	**50a**	H	H	Ph	**134a**	81
2	**50b**	Me	Me	Ph	**134b**	76
3	**50c**	H	Cl	Ph	**134c**	64
4	**50d**	NO_2	H	Ph	**134d**	73
5	**50e**	H	H	C_6H_4Me-4	**134e**	77
6	**50f**	H	H	C_6H_4Cl-4	**134f**	73

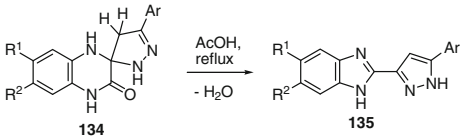
(spiro-compound **B**), (c) cleavage of the C(3)–N(4) bond (*N*-substituted 1,2-DAB **C**), (d) closure of a five-membered ring (benzimidazoline **D**), and (e) elimination of water.

3-(α-Haloarylmethyl)- and 3-(α-halophenethyl)quinoxalin-2(1*H*)-ones, as well as their various derivatives have been shown to react with α-picolines, providing high yields of 3-aryl- and 3-alkylindolizinylbenzimidazoles.

6.6 Synthesis of 2-(Pyrazol-3-yl)benzimidazoles via the Rearrangement (Use of 3-Arylacylidene-3,4-Dihydroquinoxalin-2(1*H*)-ones as Analogues of β-Diketones)

One of the most popular reactions of β-diketones in heterocyclic chemistry is the Knorr reaction, that is, the synthesis of pyrazoles by interaction of β-diketones with hydrazines. It was described that the interaction of 3-(arylacylidene)-3,4-dihydroquinoxalin-2(1*H*)-ones **50** (the schematical presentation of the 3-arylacylidene-3,4-dihydroquinoxalin-2(1*H*)-ones as analogues of β-diketones has

Table 6.15 Synthesis of 2-(pyrazol-3-yl)benzimidazoles



134 135

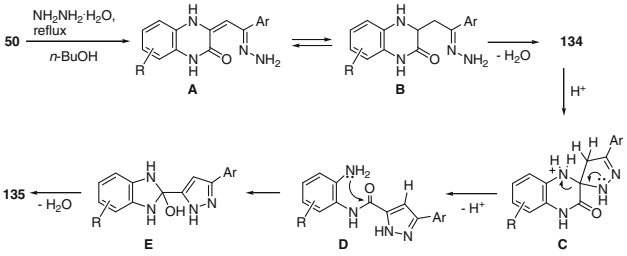
Entry	Substrate	R^1	R^2	Ar	Product	Yield (%)
1	**134a**	H	H	Ph	**135a**	99
2	**134b**	Me	Me	Ph	**135b**	99
3	**134c**	H	Cl	Ph	**135c**	98
4	**134d**	NO_2	H	Ph	**135d**	96
5	**134e**	H	H	C_6H_4Me-4	**135e**	99
6	**134f**	H	H	C_6H_4Cl-4	**135f**	85

been shown in Sect. 6.2.3(E) (see Fig. 6.3, structure **50**)) with hydrazine hydrate in boiling butanol solution proceeds with the formation of 3′-aryl-1,2,3,4,4′,5′-hexahydro[quinoxalin-2,5′-pyrazol]-3-ones **134a–f** in good yields (Table 6.14) (Mamedov et al. 2009a, 2010b; Murtazina 2010).

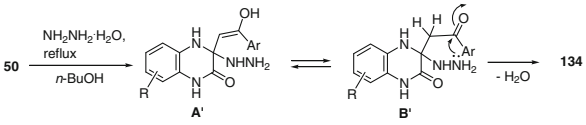
Boiling spiro-quinoxalin-2,5′-pyrazol-3-ones **134a–f** in an acetic acid solution for 8 h results in the acid catalysis rearrangement with the release of water and the formation of corresponding 2-(pyrazol-3′-yl)benzimidazoles in quantitative yields (Table 6.15).

Thus, both the formation of spiro-quinoxalinones **134a–f** and their rearrangement into the corresponding pyrazolylbenzimidazoles **135a–f** proceed in high yields (Tables 6.14 and 6.15). As is evident from the structure of compounds **135a–f**, the C(2)–C(3) = CH–C(O)–Ar fragment of quinoxalines **50a–f** and hydrazine hydrate are involved in the formation of the heterocyclic systems.

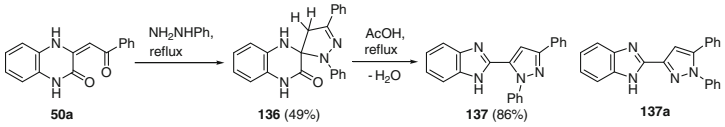
On the basis of the known chemistry of hydrazines (Audrieth and Ogg 1951; Buckingham 1969; Behforouz et al. 1985), ketones (Smith 2013b; Gutsche 1967), and quinoxalinones (Cheeseman and Cookson 1979) it is reasonable to assume that the first stage of the reaction mechanism involves the addition of the hydrazine to the carbonyl group of the 3-arylacylidene fragment of quinoxalin-2(1*H*)-one **50** with the formation of intermediate **A** capable reversible tautomerization to intermediate **B**. The next step involves a nucleophilic attack of the amino group on the C(3) atom of the quinoxalin-2(1*H*)-one to form the spiro-quinoxaline derivative **134**. Rearrangement of the spiro-quinoxaline is then assumed to occur according to Scheme 6.52, which proceeds by cascade reactions involving: (a) acid-catalyzed ring-opening in spiro-compound **C** with the intermediate formation of pyrazolo-derivative **D**, (b) intramolecular nucleophilic attack by the amino group on the carbamoyl carbonyl group with the intermediate formation of hydroxy-derivative **E**, and (c) elimination of water leading to the formation of the



Scheme 6.52 Proposed mechanism of the rearrangement with the initial attack on the aroyl carbonyl group



Scheme 6.53 Proposed mechanism of the rearrangement with the initial attack on the C(3) atom of the quinoxalin-2(1*H*)-one



Scheme 6.54 Phenylhydrazine as nucleophilic reagent in the rearrangement of 3-arylacylidene-3,4-dihydroquinoxalin-2(1*H*)-one

final product **135**. It was shown that the reaction does not proceed in neutral or aprotic solvents.

It should be pointed out that the formation of spiro-quinoxaline derivative **134** could be due to the Michael addition of hydrazine to the partially positive C(3) atom of the quinoxalin-2(1*H*)-one **50** in the first stage of the reaction mechanism with the formation of intermediate **A′** capable reversible tautomerization to intermediate **B′**. Then cyclization involves the nucleophilic attack of the amino group on the carbonyl group of the 3-arylacylidene fragment of quinoxalin-2(1*H*)-one (Scheme 6.53).

It is worth noting that the reaction of phenylhydrazine with 3-arylacylidene-3,4-dihydroquinoxalin-2(1*H*)-one **50a** proceeds similarly to the reaction with hydrazine hydrate. This involves the formation of spiro-compound **136**, which rearranges into pyrazolylbenzimidazole **137**, and no other possible regioisomer **137a**, in boiling acetic acid (Scheme 6.54).

This was accomplished via a novel quinoxalinone-benzimidazole rearrangement of 3-arylacylidene-3,4-dihydroquinoxalin-2(1*H*)-ones on exposure to hydrazine hydrate and phenylhydrazine. The reaction is readily applicable to large-scale synthesis.

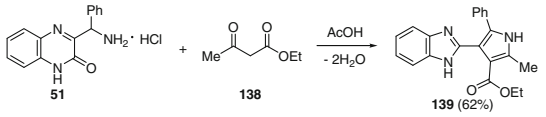
6.7 Synthesis of 2-(Pyrrol-3-yl)benzimidazole via the Rearrangement (Use of 3-α-Aminobenzylquinoxalin-2(1*H*)-ones as Analogues of α-Aminoketones)

One of the most popular reactions of α-aminoketones in heterocyclic chemistry is another Knorr reaction, that is, the synthesis of pyrroles by interaction of α-aminoketones with β-dicarbonyl compounds. This reaction was carried out (Mamedov et al. 2011a). The interaction of 3-(α-aminobenzyl)quinoxalin-2-(1*H*)-one hydrochloride **51** (the schematical presentation of the 3-α-aminobenzylquinoxalin-2(1*H*)-ones as analogues of α-aminoketones has been shown in Sect. 6.2.3(E) (see Fig. 6.3, structure **51**)) with acetoacetic ester **138** in the boiling acetic acid proceeds with the contraction of the pyrazine ring system as a result of the rearrangement involving C(2)–C(3)–C(NH_2)Ph and C(2)–C(3) fragments of the quinoxalinone system and acetoacetic ester, respectively, with the formation of 2-(5-methyl-2-phenyl-4-ethoxycarbonylpyrrol-3-yl)benzimidazole **139** (Scheme 6.55) (Mamedov et al. 2011a).

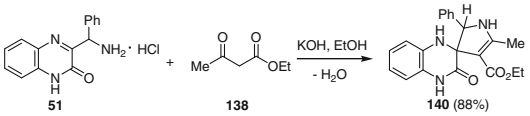
Instead of the 3-(α-aminobenzyl)quinoxalin-2-(1*H*)-one **51** hydrochloride in the reaction with acetoacetic ester **138** its free base is used. This has no significant effect on the yield of the product of the rearrangement, which is apparently associated with the occurrence of various acid-catalyzed side reactions involving acetoacetic ether.

To improve the yield of the product of the rearrangement, we referred to the main principle of this rearrangement, as proposed above (Sect. 6.2.3.D).

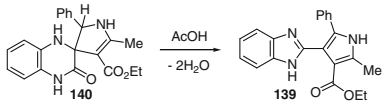
In accordance with the above principle the spiro[4-pyrrolyne-3,2′-quinoxalin]-3′(4′*H*)-one **140** was synthesized. The 3-(α-aminobenzyl)quinoxalin-2(1*H*)-one **51** was considered to be the hetero analogue of α-aminocarbonyl compound according to the Knorr reaction (Knorr 1884; Castro et al. 1970; Mironov et al. 1973) (i.e., obtaining pyrroles by the condensation of α-aminoketones with ketones containing an activated methylene group). Thus, at position 2 of quinoxalinone **51** we have set up the necessary pyrrolydine system with the help of the reaction of the compound **51** with acetoacetic ester **138** in EtOH in the presence of KOH. The reaction



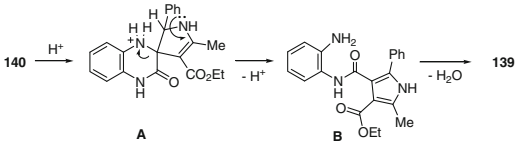
Scheme 6.55 The rearrangement of 3-(α-aminobenzyl)quinoxalin-2-(1*H*)-one hydrochloride in the reaction with acetoacetic ester



Scheme 6.56 The synthesis of spiro[4-pyrrolyne-3,2′-quinoxalin]-3′(4′*H*)-one



Scheme 6.57 Acid-catalyzed rearrangement of spiro[4-pyrrolyne-3,2′-quinoxalin]-3′(4′*H*)-one **140**



Scheme 6.58 Proposed mechanism of the rearrangement

proceeds smoothly with the formation of the desired spiro-compound–5-methyl-2-phenyl-4-ethoxycarbonyl-1′*H*-spiro[4-pyrrolyne-3,2′-quinoxalin]-3′(4′*H*)-one **140** with high yields (88 %) (Scheme 6.56). It should be noted that the reaction proceeds well enough both at room temperature (12 h) and by reflux (4 h).

Boiling the compound **140** in acetic acid for 1 h leads to the expected benzimidazole **139** in quantitative yields (Scheme 6.57).

The formation of the rearrangement product in the reaction of 3-(α-aminobenzyl) quinoxalin-2(1*H*)-one **51** with acetoacetic ester can be represented as shown below in the Scheme 6.58. According to the scheme, the formation of spiro-compound **140** occurs at the initial stage. In reaction conditions it further undergoes acid-catalyzed rearrangement. The latter involves the disclosure of the pyrazine ring of the quinoxalin-2(1*H*)-one system on the N(1)–C(2) bond in the intermediate salt **A** and the closure of the imidazole ring of the benzimidazole system with the newly formed amino group and the carbonyl group of carbamoyl fragment in the pyrrole derivative **B** (Scheme 6.58).

It should be pointed out that other substituted derivatives of 3-(α-aminobenzyl) quinoxalin-2(1*H*)-one also successfully react not only with acetoacetic ester but with other esters of β-oxoacids, resulting in corresponding derivatives of 2-(pyrrol-3-yl)benzimidazole in high yields.

6.8 Synthesis of 2-(Benzimidazol-2-yl)quinolines via the Rearrangement (Use of 3-Methylquinoxalin-2(1*H*)-ones as Analogues of Usual Ketones)

One of the most popular reactions of usual ketones in the heterocyclic chemistry is the Friedländer reaction, that is, the synthesis of quinolines by their interaction with *o*-acylarylamines in basic or acid catalysis conditions.

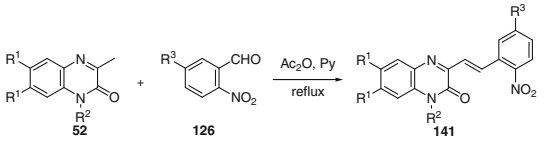
This reaction has been modified according to the system based on aromatic aldehydes **126** and 3-methylquinoxalinones **52** (the schematical presentation of the 3-methylquinoxalin-2(1*H*)-ones as analogues of usual ketones has been shown in Sect. 6.2.3(E) (see Fig. 6.3, structure **52**)), easily available from methylpyruvates and 1,2-DABs. The first stage of their modification involves the formation of *o*-nitrostyryl derivatives of quinoxalin-2(1*H*)-one **141** (Scheme 6.59) (Mamedov et al. 2010c).

The second stage is based on the reduction of *o*-nitrostyryl derivatives **141** when exposed to $Na_2S_2O_4$ (Sodium hydrosulfate, Sodium dithionate). *o*-Aminonitrostyryl derivatives of quinoxalin-2(1*H*)-one, obtained in these conditions immediately undergo acid-catalyzed rearrangement with the formation of corresponding benzimidazolyl quinoline derivatives. As is evident from the structure of compounds **142**, the C(2)–C(3) fragment and the β-2-nitrostyryl substitute at position 3 of the quinoxalin-2(1*H*)-one system are involved in constructing two new heterocyclic systems (Table 6.16).

This reaction also proceeded with a compound **141j** possessing two 3-(β-2-nitrostyryl)quinoxalin-2(1*H*)-one fragments, with the formation of a benzimidazole-monopodand with terminal benzimidazole fragments at C(2) and C(2′) positions of the quinoline ring system (Scheme 6.60).

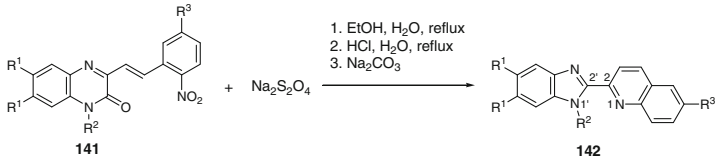
To investigate the reaction mechanism, the reduction of 3-(β-2-nitrostyryl)-6,7-dimethylquinoxalin-2(1*H*)-one **141h** with hydrogen using a 10 mol% $Pd/CaCO_3$ as the catalyst in methanol has been performed and obtained the corresponding 3-(β-2-aminostyryl)-6,7-dimethylquinoxalin-2(1*H*)-one **143h**. When boiled in AcOH for 3 h the latter was transformed into 2-(benzimidazol-2-yl) quinoline **142h** (Scheme 6.61).

On the basis of the known chemistry of aniline (Ham 1964; Zhu and Zhang 2004; Byun et al. 2007; Parvatkar et al. 2009; Marco-Contelles et al. 2009; Bian et al. 2010; Newhouse et al. 2010), azadienes (Bouaziz et al. 1995; Gouverneur and

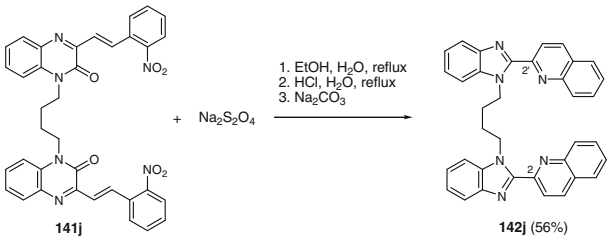


Scheme 6.59 Synthesis of 3-(β-2-nitrostyryl)quinoxalin-2(1*H*)-ones

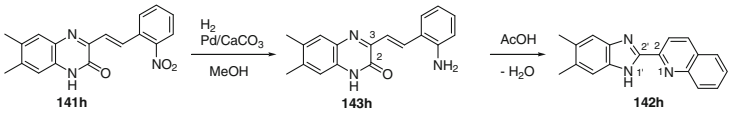
Table 6.16 One-pot synthesis of 2-(benzimidazol-2-yl)quinolines from 3-(β-2-nitrostyryl)-quinoxalin-2(1*H*)-ones



Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)
1	**141a**	H	H	H	**142a**	80
2	**141b**	H	Me	H	**142b**	76
3	**141c**	H	Et	H	**142c**	74
4	**141d**	H	*n*-Pr	H	**142d**	53
5	**141e**	H	*n*-Bu	H	**142e**	69
6	**141f**	H	*n*-Pent	H	**142f**	70
7	**141g**	H	*n*-Hex	H	**142g**	54
8	**141h**	Me	H	H	**142h**	79
9	**141i**	H	H	Cl	**142i**	59

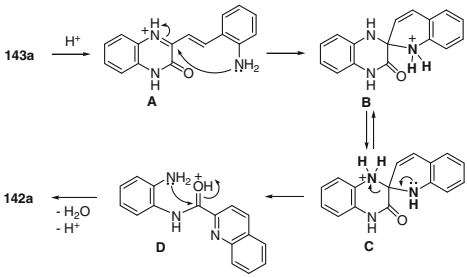


Scheme 6.60 Synthesis of 1,4-*bis*[2-(quinolin-2-yl)-1*H*-benzimidazol-1-yl]butane



Scheme 6.61 Synthesis of 2-(benzimidazol-2-yl)quinoline from 3-(β-2-nitrostyryl)-6,7-dimethylquinoxalin-2(1*H*)-one via corresponding amino derivative

Ghosez 1996; Palacios and Rubiales 1996; Motortna and Grierson 1999; Cuellar et al. 2002; Berry and Hsung 2004; Bandini et al. 2010), and quinoxalinones (Cheeseman and Cookson 1979; Mamedov et al. 2005b), it is reasonable to assume that the first stage of this reaction involves the nucleophilic attack of the amine group on the C(3) atom of the quinoxalin-2(1*H*)-one of **A** to form the



Scheme 6.62 Proposed mechanism of the rearrangement

spiro-quinoxaline derivative **B**. Rearrangement of the spiro-quinoxaline is then assumed to occur according to Scheme 6.62 by cascade reactions involving: (a) acid-catalyzed ring-opening with cleavage of the C(3)–N(4) bond in the spiro-compound **C** leading to the formation of the quinoline derivative **D**, and (b) intramolecular nucleophilic attack by the amino group on the carbamoyl carbonyl group with the formation of the final product **142** following the elimination of water.

This protocol includes a novel acid-catalyzed rearrangement of 3-(β-2-aminostyryl)quinoxalin-2(1*H*)-ones. The simplicity of the reaction design and the possibility of introducing a variety of substituents at any position of both the benzimidazole and quinoline ring systems make this method a useful tool for constructing these medicinally and technically (organic emitting materials) relevant compounds. The reaction is readily applicable to large-scale synthesis.

6.9 Synthesis of 4-(Benzimidazol-2-yl)quinolines via the Rearrangement (Use of 3-(2-Aminophenyl) quinoxalin-2(1*H*)-ones as Aromatic *o*-Aminoaldehydes (or Ketones)

6.9.1 Synthesis of Structurally Diverse Quinoline Derivatives with Benzimidazole Moieties

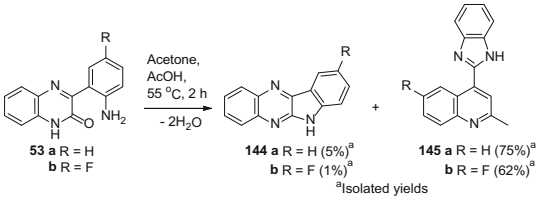
It has been also shown that 3-(β-2-nitrostyryl)quinoxalin-2-(1*H*)-ones **141** are easily obtained from 3-methylquinoxalin-2(1*H*)-one **52** and *o*-nitrobenzaldehyde **126**, and when exposed to sodium dithionite are converted into 2-(benzimidazol-2-yl) quinolines **142** (Mamedov et al. 2010c). The process occurs under reduction conditions in a cascade of the modified Friedländer reaction and the new acid-catalyzed rearrangement through the intermediately formed products–3-(β-2-aminostyryl) quinoxalin-2(1*H*)-ones **143** (Scheme 6.60).

As can be seen from the structure of the compound **142**, the *o*-aminostyryle substituent and the C(2), C(3) atoms of the amide and imine fragments of the pyrazine ring of quinoxalin-2(1*H*)-one **143** (Scheme 6.61) are involved in the construction of two new heterocyclic systems. In this case, the formation of the pyridine ring of the quinoline system occurs as a result of the proceeding new rearrangement (Hassner and Namboothiri 2012; Mamedov and Zhukova 2013). As can be seen from Table 6.16, the atoms C(2) and C(3) of the quinoxalin-2(1*H*)-one system become the atoms C(2′) and C(2) of the benzimidazole and quinoline systems of the compounds **142** respectively.

Following the logics described in the papers (Mamedov et al. 2006, 2008a, b, 2009a, 2010a, b, c, 2011a, b, c, 2012, 2013; Kalinin et al. 2007) and specifically in the paper (Mamedov et al. 2010c) on the new rearrangement of the quinoxalin-2(1*H*)-one derivatives, we assumed that in the latter reaction 3-(2-aminophenyl) quinoxalin-2(1*H*)-one derivatives **53** (the schematical presentation of the 3-(2-aminophenyl)quinoxalin-2(1*H*)-ones as aromatic *o*-aminoaldehydes (or ketones) has been shown in Sect. 6.2.3(E) (see Fig. 6.3, structure **53**)) can be used instead of 3-methylquinoxalin-2(1*H*)-one **52** and *o*-nitrobenzaldehyde **126** derivatives as the hetero analogues of *o*-aminoaromatic aldehydes and ketones bearing an active α-methylene functionality. The ketones can be condensed with compounds **53** capable of providing a two-carbon fragment in the construction of the quinoline system, which makes it possible to synthesize the 4-(benzimidazol-2-yl)quinolines **145**,**147**,**149** isomeric to the 2-(benzimidazol-2-yl)quinolines **142**.

To optimize the process, it was initially carried out the reaction of 3-(2-aminophenyl)quinoxalin-2(1*H*)-one **53a** with acetone in acetic acid with various ratios of reagents and different reaction times. Regardless of the molar ratio of the reagents (1:32, 1:16, 1:8, 1:4; **53a**:**acetone**) and the reaction time (6, 4, or 2 h) the reaction proceeded in the same way with the formation of the ∼ 85 % yield of the crude product, which contains ∼90 % of the quinoline **145a** and ∼10 % of the qunoxaline **144a** derivatives on the basis of the ^{1}H NMR spectrum (Scheme 6.63) (Mamedov et al. 2014c, d; Galimullina 2015).

The first product is formed as a result of the rearrangement, whereas the second one is the result of the intramolecular cyclocondensation of the quinoxaline derivative **53a**. The optimal temperature conditions for this reaction approximately correspond to the boiling temperature of acetone (55 °C). This temperature condition appears to be optimal for the reaction of 3-(2-aminophenyl)quinoxalin-2



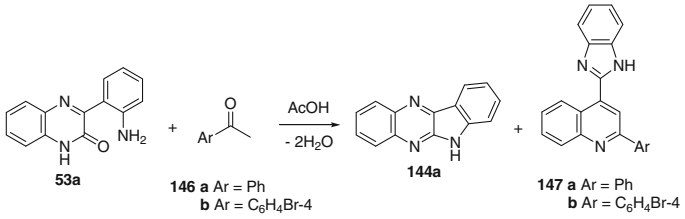
Scheme 6.63 The reaction of 3-(2-aminophenyl) quinoxalin-2(1*H*)-ones derivatives **53a**, **b** with acetone

(1*H*)-one **53a** with acetophenone **146a** and 4-bromoacetophenone **146b**. As can be seen from Table 6.17 the optimal ratio in these cases is 1:2 (**53a**:**146a** and **53a**:**146b**) when the reactions are carried out for 5 h (entries 4 and 9), because when the ratio of the reagents was 1:1 there occurred the increase in the yield of compound **144a** and the decrease in the overall yield of the mixture of compounds **144a** and **147a**, **b** (entries 1, 6, and 7). When the ratio of the starting compounds was 1:10 or 1:5 (entries 5 and 10) in spite of the satisfactory yield of the desired product, there appeared some difficulties in the purification of the final products.

To explore the scope and limitations of the reaction, the procedure was extended to 3-(2-amino-5-fluorophenyl)quinoxalin-2(1*H*)-one **53b** and various acetophenones **146a–f**. As indicated in Table 6.18, the reactions proceeded very efficiently, and led to the formation of the corresponding 4-(benzimidazol-2-yl)quinolines **147a–l** as major and 6*H*-indolo[2,3-*b*]quinoxaline **144a**, **b** as minor products.

Based on the known chemistry of amines (Smith 2001), enolizable ketones (Wang 2009), enamines (Rappoport 1994; Hickmott 1982a, b, 1984), quinoxalinones (Cheeseman and Cookson 1979), and the previous reports (Mamedov et al. 2006, 2008a, b, 2009a, 2010a, b, 2011a, b, 2012, 2013; Kalinin et al. 2007; Mamedov and Murtazina 2011; Mamedov and Zhukova 2013) a plausible mech-

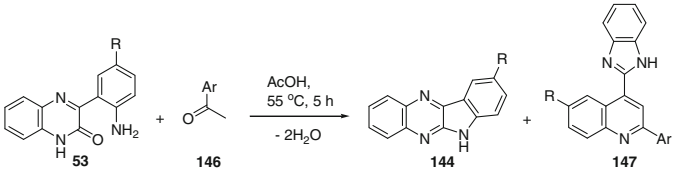
Table 6.17 Optimization of the reaction conditions



Entry	Substrate	Ratio **53a/146**	Temp. (°C)	Time (h)	Products	Ratio **144a/147**[a]	Total yield (%)
							144a + 147
1	**146a**	1/1	55	2	**144a + 147a**	20/80	54
2	**146a**	1/2	reflux	2	**144a + 147a**	15/85	52
3	**146a**	1/2	55	2	**144a + 147a**	12/88	75
4	**146a**	1/2	55	5	**144a + 147a**	15/85	95
5	**146a**	1/10	55	5	**144a + 147a**	15/85	80
6	**146b**	1/1	55	2	**144a + 147b**	8/92	40
7	**146b**	1/1	55	6	**144a + 147b**	8/92	46
8	**146b**	1/2	55	2	**144a + 147b**	5/95	79
9	**146b**	1/2	55	5	**144a + 147b**	4/96	86
10	**146b**	1/5	55	5	**144a + 147b**	4/96	72

[a]Estimated on the basis of ^{1}H NMR spectra of the reaction mixture

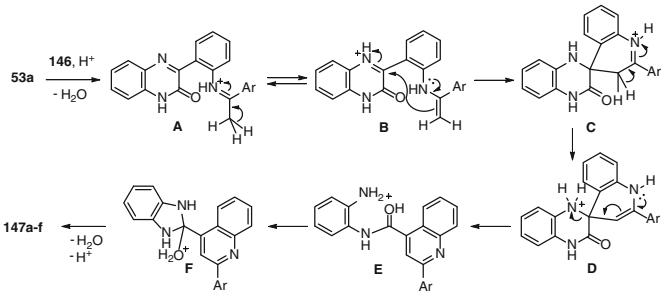
Table 6.18 Reaction of 3-(2-aminophenyl)-quinoxalin-2(1*H*)-ones **53a**, **b** with acetophenones **146a–f**



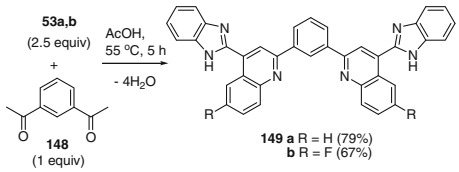
Entry	**53**	R	**146**	Ar	Products	Yield (%)	
						144	**147**
1	**53a**	H	**146a**	Ph	**144a** + **147a**	6	80
2	**53a**	H	**146b**	C_6H_4Br-4	**144a** + **147b**	4	76
3	**53a**	H	**146c**	C_6H_4Br-3	**144a** + **147c**	4	78
4	**53a**	H	**146d**	C_6H_4Br-2	**144a** + **147d**	4	73
5	**53a**	H	**146e**	C_6H_4Cl-4	**144a** + **147e**	4	77
6	**53a**	H	**146f**	C_6H_4Cl-2	**144a** + **147f**	4	71
7	**53b**	F	**146a**	Ph	**144b** + **147g**	1	68
8	**53b**	F	**146b**	C_6H_4Br-4	**144b** + **147h**	1	66
9	**53b**	F	**146c**	C_6H_4Br-3	**144b** + **147i**	1	64
10	**53b**	F	**146d**	C_6H_4Br-2	**144b** + **147j**	1	61
11	**53b**	F	**146e**	C_6H_4Cl-4	**144b** + **147k**	2	65
12	**53b**	F	**146f**	C_6H_4Cl-2	**144b** + **147l**	1	62

anism for the reaction of the formation of 4-(benzimidazol-2-yl)quinolines **147** has been proposed (Scheme 6.64). The reaction starts with the condensation of ketones with 3-(2-aminophenyl)quinoxalin-2(1*H*)-one **53a** to form imine **A**, which is transformed to intermediate **B** by tautomerization. Subsequently intermediate **B** is easily cyclized through the intramolecular nucleophilic addition to give the spiro-quinoxaline derivative **C**. The rearrangement of the spiro-quinoxalinone **C** is then assumed to occur according to Scheme 6.64, which proceeds by cascade reactions involving: (a) the ring-opening with the cleavage of the C(3)–N(4) bond in the spiro-compound **D** with the intermediate formation of the quinoline derivative **E**, (b) the intramolecular nucleophilic attack by the amino group on the carbonyl group with the intermediate formation of the hydroxy-derivative **F**, and (c) the elimination of water leading to the formation of the final product **147**. All the stages of the reaction include acid-catalyzed processes.

It was studied the scope of the methodology, first with respect to the 1,3-diacetylbenzene **148** (Scheme 6.65). As can be seen, this chemistry is not limited to mono- and disubstituted systems, and a compound with two acetyl fragments is an acceptable substrate as well.



Scheme 6.64 A plausible mechanism for the formation of 4-(benzimidazol-2-yl)quinolines **147**



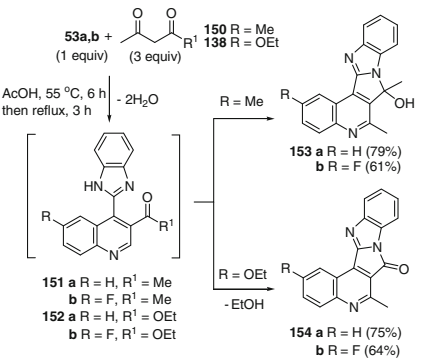
Scheme 6.65 Reaction of 3-(2-aminophenyl)quinoxalin-2(1*H*)-ones **53a**, **b** with 1,3-diacetylbenzene **148**

6.9.2 *Synthesis of Benzimidazolo[2,1-a]pyrrolo[3,4-c] quinolines*

The scope of this chemistry was also investigated with respect to the compounds with two same and different carbonyl groups in their compositions. The 3-(2-aminophenyl)quinoxalin-2(1*H*)-ones **53a**, **b** were allowed to react with 1,3-pentanedione **150** and ethyl acetoacetate **138**, in AcOH (Scheme 6.66). The isolated yields of the products are all high, as well but there occurs the formation of benzimidazolo[2,1-*a*]pyrrolo[3,4-*c*]quinoline derivatives **153a**, **b** and **154a**, **b** instead of the expected 4-(benzimidazol-2-yl)quinolines **151a**, **b** and **152a**, **b** correspondingly, with acetyl and ester groups at position 3 of the quinoline system (Mamedov et al. 2014c, d).

The formation of pentacyclic condensed systems **153a**, **b** and **154a**, **b** can be due to the intramolecular nucleophilic addition of the nitrogen atom of the benzimidazole system to the carbonyl group of the substituents at position 3 of the quinoline system of compounds **151a**, **b** and **152a**, **b**. In this case, compounds **152a**, **b** with the acetyl group provided the formation of alcohols **153a**, **b**, while compounds **152a**, **b** with the ester group provided the formation of ketones **154a**, **b**.

Thus, an efficient synthesis for structurally diverse 4-(benzimidazol-2-yl) quinolines via reactions of 3-(2-aminophenyl)quinoxalin-2(1*H*)-ones and ketones, including acetone, acetophenones, 1,3-pentanedione and ethyl acetoacetate has been developed. The selective formation of the very different quinoline derivatives



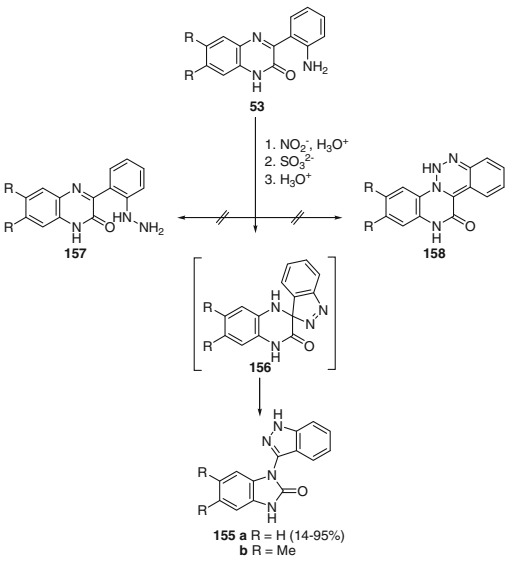
Scheme 6.66 Reaction of 3-(2-aminophenyl)quinoxalin-2(1*H*)-ones **53a**, **b** with acetylacetone **150** and ethyl acetoacetate **138**

depends on the structure of ketones. The key steps are assumed to involve the new acid-catalyzed rearrangement of the spiro-quinoxalinone derivatives formed in situ from the reaction of 3-(2-aminophenyl)quinoxalin-2(1*H*)-ones and ketones under the modified Friedländer reaction. This transformation would facilitate the synthesis by short reaction times, large-scale synthesis, simple, and prompt isolation of the products, which are the main advantages of this procedure.

6.9.3 *Synthesis of 1-(1*H*-Indazol-3-yl)-1*H*-benzimidazol-2(3*H*)-one*

It should be pointed out that in an attempt to prepare 3-(2-hydrazinophenyl) quinoxalin-2(1*H*)-one **157** by reduction of corresponding diazonium salt from 3-(2-aminophenyl)quinoxalin-2(1*H*)-ones **53** with sodium sulfite, instead of the intended product **157** a compound with the molecular formula $C_{14}H_{10}N_4O$ has been isolated, which the authors (Wiedermannová et al. 2003) considered to be 6*H*-quinoxalino[1,6-*c*][1,2,3]benzotriazin-13(12*H*)-one **158**. However, later (Lučka et al. 2007) it was proved that the structure proposed by the authors (Wiedermannová et al. 2003) was incorrect. By NMR spectroscopy (Lučka et al. 2007) and by X-ray analysis (Fryšová et al. 2011) it was shown that the correct structure is 1-(1*H*-imidazol-3-yl)-1*H*-benzimidazol-2(3*H*)-one **155** (Scheme 6.67).

The formation of the 1*H*-benzimidazol-2(3*H*)-one derivative **155** as a consequence of the principle suggested above proceeds through the spiro-compound **156** without any mobile hydrogen atom in their spiro-forming component.

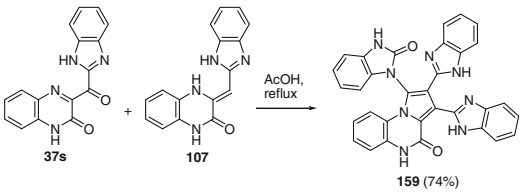


Scheme 6.67 Rearrangement of 3-(2-aminophenyl)quinoxalin-2(1*H*)-ones under the condition of the synthesis of corresponding diazonium salts

6.10 Synthesis of 1-Pyrrolylbenzimidazolones via the New Rearrangements (Use of 3-Aroyl-, 3-Alkanoyl- and 3-Hetaroylquinoxalin-2(1*H*)-ones as Analogues of α-Diketones)

*6.10.1 Synthesis of 2,3-Di(1*H*-benzimidazol-2-yl)-1-(1*H*-benzoimidazol-2-on-1-yl)pyrrolo[1,2-a]quinoxalin-4(5*H*)-one*

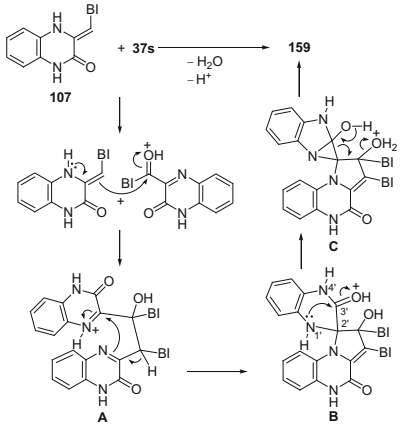
Returning to the synthesis of 2,3-*bis*(benzimidazol-2-yl)quinoxalines **100a–g** (Scheme 6.41; Table 6.5) it should be noted that in one case, i.e., in the case of the synthesis of 2,3-*bis*(benzimidazol-2-yl)-6-nitroquinoxaline **100e**, the less-reactive 1,2-diamino-4-nitrobenzene **5h** was used as a reagent. In this case a derivative of pyrrolo[1,2-*a*]quinoxaline containing one benzimidazolone (in position 1) and two benzimidazole (at positions 2 and 3) fragments in the newly formed pyrrole ring from the reaction mixture were isolated in trace amounts as an unexpected product. The formation of compound **159** could be due to the condensation of 3-(benzimidazo-2-yl) quinoxalin-2(1*H*)-one **37s** with its predecessor–3-(benzimidazol-2-yl)methylene-



Scheme 6.68 The formation of 1-(benzimidazol-2-on-1-yl)-2,3-(dibenzimidazol-2-yl)pyrrolo-[1,2-*a*]quinoxalin-4(5*H*)-one **159**

quinoxalin-2(1*H*)-one **107** (the schematical presentation of the 3-hetaroylquinoxalin-2(1*H*)-ones as analogues of α-diketones has been shown in Sect. 6.2.3(E) (see Fig. 6.3, structure **37**)), which is present as an impurity in compound **37s**, used in the reaction with 1,2-diamino-4-nitrobenzene **5h**. Indeed, carrying out the reaction of 3-(benzimidazo-2-yl)quinoxalin-2(1*H*)-one **37s** with 3-(benzimidazol-2-yl)methylenequinoxalin-2(1*H*)-one **107** in boiling AcOH led to the derivative of pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **159** in a good yield (Scheme 6.68) (Mamedov et al. 2013).

As can be seen in Scheme 6.69, the formation of compound **159** occurs as a result of a cascade reaction involving: (a) the intermolecular ene reaction (Naruse et al. 2005; Hilt and Treutwein 2007; Shen et al. 2009) between the enamine **107** and ketone **37s** with the formation of compound **A**, (b) the intramolecular ene reaction (Oppolzer et al. 1973; Keck and Webb 1979, 1981) with the formation of the spiro-derivative quinoxalinono[2′,1]pyrrolo[1,2-*a*]quinoxaline **B**, and (c) a new



Scheme 6.69 A plausible mechanism for the formation of pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one **159**

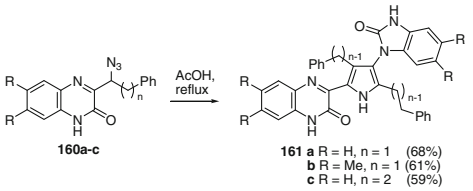
quinoxalinono-benzimidazolone rearrangement in the spiro-forming fragment. Unlike the rearrangements discussed above (Sects. 6.2.2 and 6.4–6.9), in which the opening of the pyrazine ring of the quinoxalinone system of spiro-derivative (Schemes 6.14, 6.46, 6.47, 6.51, 6.52, 6.58, 6.62, 6.64) occurs between the C(3) and N(4) atoms, the opening of the pyrazine ring of the quinoxaline system of spiro-derivative **B** occurs in the new rearrangement between the C(2) and C(3) atoms, through the intermediate formation of fused spiro-aziridino[2′,1]pyrrolo[1,2-*a*]quinoxaline **C** (Scheme 6.69).

In this case 3-(benzimidazo-2-yl)quinoxalin-2(1*H*)-one **37s**, supplying two carbon atoms in the formation of the pyrrole ring is subjected to a rearrangement (Scheme 6.68) different from that discussed above (Sect. 6.4.2).

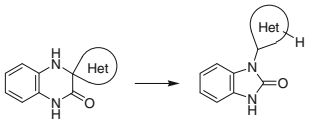
6.10.2 *Synthesis of 3-[(3,5-Disubstituted-4-(1*H*-benzimidazol-2-on-1-yl)-1*H*-pyrrol-2-yl]quinoxalin-2(1*H*)-ones*

The above rearrangement was observed earlier (see Saifina thesis pp. 89–93 in Chap. 4) in the example of the self-condensation of 3-(α-azidophenylalkyl) quinoxalin-2(1*H*)-ones **160a–c** (Scheme 6.70) (Saifina 2009).

The fact that the formation of the benzimidazolone derivatives in the reactions of the self-condensation of 3-(α-azidophenylalkyl)quinoxalin-2(1*H*)-ones **160** (Scheme 6.70) (Saifina 2009) and in the condensation of 3-(benzimidazo-2-yl) quinoxalin-2(1*H*)-one **37s** with its predecessor–3-(benzimidazol-2-yl)methylene-quinoxalin-2(1*H*)-one **107** (Scheme 6.68) gives reason to propose a new hypothesis, that "*any of the spiro-derivatives of 1,2,3,4-tetrahydroquinoxalin-3-one without any mobile hydrogen atom in their spiro-forming component are on their way to the benzimidazolone derivative with the spiro-forming component at position 1*" (Scheme 6.71).



Scheme 6.70 A new quinoxalinone-benzimidazolone rearrangement proceeding under self-condensation of 3-(α-azidophenylalkyl)quinoxalin-2(1*H*)-ones



Scheme 6.71 A schematic presentation of the spiro-1,2,3,4-tetrahydroquinoxalin-3-one →benzimidazolone rearrangement

6.10.3 Synthesis of 1-Pyrrolylbenzimidazolones from Quinoxalinones and Enamines Generated In Situ from Ketones and Ammonium Acetate

In 2011, it has been reported annulation/ring-opening/ring-closure reactions of 3-functionally substituted quinoxalinones promoted by arylmethanediamines (*N*,*N*-1,3-binucleophilic reagents generated in situ from ammonium acetate and corresponding aldehyde) in which structurally different imidazole derivatives could be obtained in high yields (Mamedov et al. 2011b).

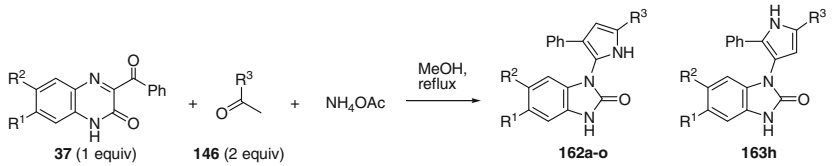
During the studies on the ring-opening/ring-closing reactions of 3-BQs (Mamedov et al. 2008a, b, 2009a, 2011a, b, c, 2012; Mamedov and Murtazina 2011; Mamedov and Zhukova 2013), it has been attempted to use enamines (generated in situ from ammonium acetate and corresponding methylaryl(hetaryl)ketones) as an alternative source of the *N*,*C*-1,3-binucleophilic reagents. Interestingly, it was found that when conducting the reaction of 3-BQ **37a** with enamines as *N*,*C*-1,3-binucleophilic reagents in refluxing MeOH as a solvent, compound **162a** was formed rather than the desired and expected product(s). Apparently, as a result there appeared a product with two newly formed heterocyclic systems. Herein, this novel enamine-mediated rearrangement of 3-BQs in MeOH, which proceeds through the ring-closure/ring-opening/ring-closure dual cleavage of the C(3)=N(4) and C(2)–C(3) bonds has been presented (Mamedov et al. 2015).

The examination in detail of the reaction conditions for the 3-BQ **37a**, acetophenone **146b** with NH_4OAc in MeOH shows that the yield of **162b** was achieved with a maximum (81 %) when the reaction was carried out with the use of reagents **37a/146b**/NH_4OAc in the ratio of 1:2:15 at boiling MeOH for 14 h.

With the optimized conditions in hand, the generality of the reaction was evaluated. A range of substrates with varying substituents were synthesized and investigated under standard conditions.

As can be seen from Table 6.19, the result does not depend on the nature of the substituent in acetophenones, no matter whether it is a donor or an acceptor group. For acetophenones with electron-withdrawing halogen atoms at *p*- and *m*-positions of the benzene ring and even with a strongly electron-withdrawing nitro-group as well as with a electron-donating methoxy-group, the reaction proceeded smoothly and resulted in the desired products **162b**, **c**, **e**, **g**, **h** in high (entries 2, 5 and 8) and moderate (entries 3 and 7) yields. However, it should be pointed out that in the case of **146h** with a strongly electron-donating methoxy-group, the

Table 6.19 Synthesis of 1-(pyrrolyl)benzimidazolones

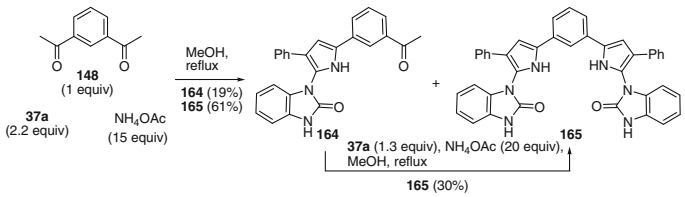


Entry	**37**	R^1	R^2	**146**	R^3	Time (h)/ NH_4OAc (equiv)	Product	Yield (%)
1	**37a**	H	H	**146a**	Ph	20/20	**162a**	65
2	**37a**	H	H	**146b**	C_6H_4Br-4	14/15	**162b**	81
3	**37a**	H	H	**146c**	C_6H_4Br-3	20/20	**162c**	66
4	**37a**	H	H	**146d**	C_6H_4Br-2	20/20	**162d**	62
5	**37a**	H	H	**146e**	C_6H_4Cl-4	14/15	**162e**	79
6	**37a**	H	H	**146f**	C_6H_4Cl-2	20/0	**162f**	63
7	**37a**	H	H	**146 g**	$C_6H_4NO_2$-3	20/20	**162g**	59
8	**37a**	H	H	**146 h**	C_6H_4OMe-4	14/15	**162h** + **163h**	92[a]
9	**37a**	H	H	**146i**	Py-2	20/20	**162i**	79
10	**37a**	H	H	**146j**	Py-3	20/20	**162j**	73
11	**37a**	H	H	**146 k**	Py-4	20/20	**162k**	76
12	**37u**	CO_2H	H	**146a**	Ph	14/15	**162l**	62
13	**37u**	CO_2H	H	**146b**	C_6H_4Br-4	14/15	**162m**	84
14	**37t**	COPh	H	**146b**	C_6H_4Br-4	24/25	**162n**	12[b]
15	**37x**	Me	Me	**146b**	C_6H_4Br-4	24/25	**162o**	63

[a]Formed two isomers in a 63:37 percentage ratio (based on ^{1}H NMR)
[b]55 % of **37t** was recovered

regioisomeric product **163h** is formed along with the main product of the reaction **162h** as well, in a percentage ratio of 63:37 in favor of the former (entry 8). This is due to the occurrence of the competing direction of the processes with the benzoyl carbonyl group at the initial stage of the reaction (Scheme 6.72, *Pathway II*). When the electron-withdrawing halogen atoms (Cl or Br) were located at one *o*-position of the benzene ring, the desired products **162d** and **162f** were obtained in good yields (entries 4 and 6). This is apparently not due to the electronic effects of these groups, and to the spacing effect, as in the cases of reactions 2-, 3- and 4-acetylpyridines. Regardless of the position of the nitrogen atom in the pyridine ring the yields of the desired products are higher (entries 9–11).

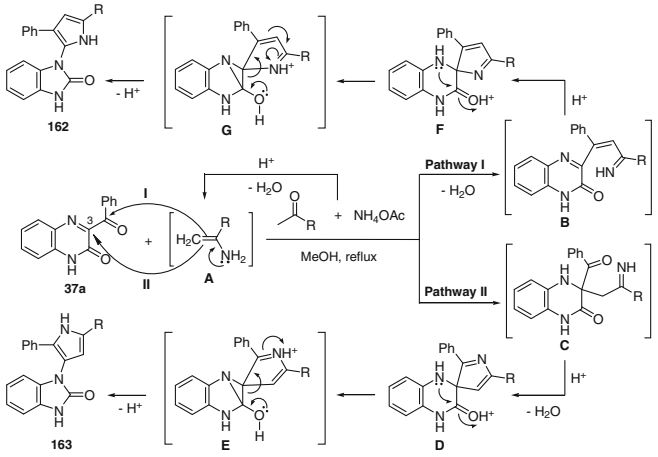
Table 6.19 reports the structural variations which are tolerated by this new multicomponent reaction (MCR). Acetophenones (electron-withdrawing and electron-donating substituents) and heteroaromatic ketones have resulted in the corresponding products in good to excellent yields. The same is true for the different 3-BQs with various substituents (entries 12–15) involving functional CO_2H (entries 12 and 13) and 6,7-dimethyl (entry 15) groups with the exception of the PhC(O) group (entry 14) in the benzene ring of the quinoxalin-2(1*H*)-one system.



Scheme 6.72 Synthesis of compounds with one and two 1-(pyrrol-2-yl)benzimidazolone structural blocks

Having developed this novel methodology for the diversification of the method and displayed its general applicability it has been provided the benzimidazol-2-one and pyrrole heterocyclic cores in one concise straightforward step. Their next goal was to build the complexity of final products and to gain access to more elaborated molecular scaffolds. Consequently, their studies were directed to an additional transformation capable of assembling a nitrogen-containing ring (Scheme 6.72). According to their synthetic plan (Scheme 6.72), the replacement of the commercially available acetophenone **146a** with 1,3-diacetylbenzene **148**, bearing an additional acetyl group would allow the anticipated cascade process with two MCR modifications in one pot. The reaction would proceed with the formation of an unprecedented compound **165**, with two 1-(pyrrol-2-yl)benzimidazolone cores in the benzene ring as a major product which precipitated from the reaction mixture and compound **164** as a minor product with one 1-(pyrrol-2-yl)benzimidazolone core. It has been shown that acetophenone **164** can also be transformed to **165**. The reaction of acetophenone **164** with 3-BQ **37a** in the presence of NH_4OAc (the ratio of reagents is given in the Scheme 6.72) proceeds with the formation of compound **165** with a 30 % yield. For the complete transformation of compound **164** in the reaction mixture it was necessary to perform procedures of allocation and its transformation into **165** three times (Scheme 6.72).

Although the exact mechanism of this reaction is yet unclear, a plausible reaction course is proposed on the basis of the known chemistry of ketones (Wang 2009), imines (Smith 2001), quinoxalines (Cheeseman and Cookson 1979; Brown 2004) and enamines (Hickmott 1982a, b, 1984; Rappoport 1994) in Scheme 6.73. The formation of the enamine intermediate **A** takes place at the initial stage of the reaction. Intermediate **A** reacts with the 3-BQ **37a** in two different ways (*Pathway I* and *Pathway II*) with the formation of an isomeric spiro[pyrrol-3,2′-quinoxalin]-3-one derivative **D** and a spiro[pyrrol-2,2′-quinoxalin]-3-one derivative **F** through the intermediate **C** and **B**. The latter are formed by the initially attached enamine on the benzoyl carbonyl carbon atom (*Pathway I*) and on the C(3) atom of the quinoxalinone system (*Pathway II*), correspondingly. Further, both *Pathway I* and *Pathway II* proceed by cascade reactions involving: (a) the acid-catalyzed ring closure of spiro-derivatives **D** and **F** with the formation of intermediates **E** and



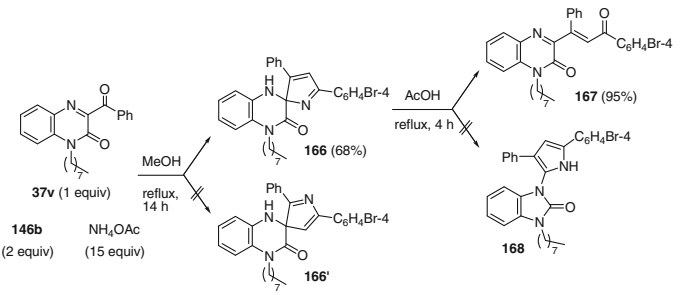
Scheme 6.73 A plausible mechanism for the formation of 1-(5-R-3-phenylpyrrol-2-yl)- **162** and 1-(5-R-2-phenylpyrrol-3-yl)- **163** benzimidazol-2(3*H*)-ones

G with the aziridine ring system; (b) the acid-catalyzed ring-opening in intermediates **G** and **E** with the formation of the final 1-(pyrrol-2-yl)- **162** and 1-(pyrrol-3-yl)benzimidazolone **163** derivatives.

It can be assumed that as in cases of the quinoxalinone-benzimidazole rearrangement (Mamedov et al. 2008a, 2010c, 2012), the use of the *N*-alkyl derivatives of quinoxalinone will provide the formation of *N*-alkylated derivatives of 1-(pyrrolyl)benzimidazolone under the conditions of rearrangement studied. However, the reaction of 3-benzoyl-1-octylquinoxalin-2-one **37v** with 4-bromoacetophenone **146b** and NH_4OAc proceeded with the formation of a spiro-derivative **166**–intermediate compound on the way to the product of rearrangement (Scheme 6.74). Changing the ratio of the reagents or the reaction time did not significantly influence the direction of the reaction. The product was identified as 5-(4-bromophenyl)-4′-octyl-2-phenyl-1′*H*-spiro[pyrrol-3,2′-quinoxalin]-3-one **166**.

Thus, there takes place the formation of only compound **166**, but not the regioisomer–5-(4-bromophenyl)-4′-octyl-2-phenyl-1′*H*-spiro[pyrrol-3,2′-quinoxalin]-3′(4′*H*)-one **166′** (Scheme 6.74). In an attempt to perform the rearrangement in boiling AcOH, compound **166** was converted to chalcone **167** with the extrusion of the nitrogen atom from the pyrrole ring. The analysis of crude products obtained from the reaction mixture after the evaporation of solvents by ^{1}H NMR spectroscopy reveals the presence of a spiro-compound **166** and a trace amount of the unreacted starting compounds (**37v** and **146b**).

The destruction of spiro-compounds takes place in the case of the *N*-octyl derivative of spiro-quinoxalinone **166**, with the release of ammonia and the formation of corresponding chalcone **167** under the rearrangement conditions (in boiling AcOH) (Scheme 6.75). It seems plausible that for the successful course of the rearrangement one of the necessary conditions is the presence of a hydrogen



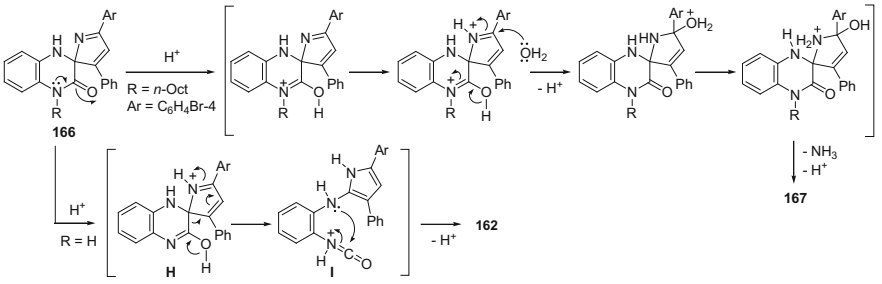
Scheme 6.74 The formation of 1′*H*-spiro[pyrrol-3,2′-quinoxalin]-3-one **166** and its acid-catalyzed conversion to chalcone **167**

atom at the nitrogen atom. Taking this into account it is possible to assume an alternative mechanism of the rearrangement in the new ring formation cascade reactions. The latter involve tautomerism (**166** to **H**) and subsequent ring opening (**H** to **I**) with the formation of the isocyanate derivative (**I**) and the ring closure (**I** to **162**) processes (Scheme 6.75). This type of ring closure is well precedented (Gibson and Green 1965; Kametani et al. 1970; Ruediger et al. 1986, Branco et al. 1992).

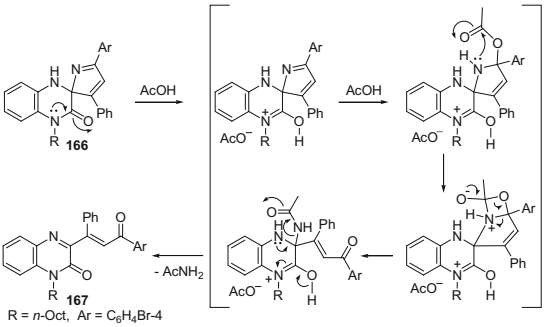
It should be pointed out that the quinoxalin-2-one/quinoxalin-2-ol tautomerism like **166** to **H**, when R = Alk, is impossible and therefore the isocyanate derivative responsible for the course of the rearrangement in the case of R = H cannot be formed (Scheme 6.75).

The formation of **167** from the spiro-quinoxalinone **166** can be presented with the AcOH as well, but in this case the pyrrole nitrogen atom of a molecule is released in the form of $AcNH_2$ (Scheme 6.76).

The formation of the benzimidazolone derivatives in the one-pot reactions of 3-BQs **37**, methylaryl(hetaryl)ketones and ammonium acetate (NH_4OAc) in methanol at reflux conditions with good to excellent yields (Table 6.19; Scheme 6.72) confirm the previously proposed hypothesis (Scheme 6.71).



Scheme 6.75 The reasonable mechanisms for the formation of (*E*)-3-(3-(4-bromophenyl)-3-oxo-1-phenylprop-1-enyl)-1-octylquinoxalin-2(1*H*)-one **167** and 1-(pyrrol-2-yl)benzimidazolones **162**



Scheme 6.76 A plausible mechanism for the formation of **167**

An important three-component reaction of 3-benzoylquinoxalinones, various methylaryl(hetaryl)ketones, and ammonia has been developed. The method described in this paper allows the preparation of substituted 1-(pyrrolyl)benzimidazolone derivatives from easily available 3-benzoylquinoxalinone precursors under multicomponent reaction conditions in the presence of various methylaryl (hetaryl)ketones and ammonia with good to excellent yields. Enamines could be generated in situ from ketones and ammonia and then smoothly react with 3-benzoylquinoxalinones to produce 1-(pyrrolyl)benzimidazolone derivatives. Using this method, we were able to assemble a wide range of benzimidazolone derivatives. An important aspect of this protocol is that it can be adapted for the synthesis of a wide range of benzimidazolone derivatives, since various methylketones are commercially available and can easily be obtained through the acylation by the Friedel–Crafts reaction. The success of this methodology encourages future exploration of related reactions.

*6.10.4 A Reaction for the Synthesis of Benzimidazol-2-ones, Imidazo[5,4-**b**]- and Imidazo[4,5-**c**]pyridin-2-ones from Quinoxalinones and Their Aza-Analogues When Exposed to Enamines*

To optimize the process, the reaction of 3-BQ **37a** with methyl 3-aminocrotonate **169a** in boiling acetic acid with various ratios of reagents (1:1, 1:5, 1:7; **37a**:**169a**) and over different reaction times was initially carried out. The optimal condition for carrying out the investigated reaction appears to be the use of reagents in a ratio of (1:7; **37a**:**169a**) in boiling acetic acid for 6 h (Mamedov et al. 2014e). Though at such ratios of the reagents the reaction proceeds successfully for 1 h, the desired products of the rearrangement are allocated easily when the reaction has been carried out for 6 h. This is apparently due to the complete decomposition or polymerization of excess enamine.

Having the optimized reaction conditions at disposal, the authors proceed to explore the scope and limitations of the reaction. The procedure was extended to 3-aroylquinoxalin-2(1*H*)-ones **37** with various substituents and methyl- (**169a**) and ethyl- (**169b**) 3-aminocrotonates. As indicated in Table 6.20, the reactions proceeded very efficiently, and led to the formation of the corresponding *N*-(pyrrol-3-yl) benzimidazol-2-ones (**170**) as major and *N*-(pyrrol-2-yl)benzimidazol-2-ones (**171**) as minor products with the overall 89–99 % yields. The reaction proceeds so fast that it appears impossible to allocate the expected spiro-compound. Under the reaction conditions we are immediately subjected to the rearrangement with the formation of *N*-pyrrolylbenzimidazol-2-ones in high yields.

A plausible reaction mechanism for the formation of *N*-pyrrolylbenzimidazol-2-ones **170** and **171** has been proposed (Scheme 6.77). The formation of *N*-pyrrolylbenzimidazol-2-ones occurs in two different ways (*Pathway I* and *Pathway II*), differing at their initial stage of the process. In the case of the formation of *N*-(pyrrol-3-yl)benzimidazol-2-ones **170** the reaction starts (Scheme 6.77, *Pathway I*) with the acid-catalyzed subsequent Michael type of the reaction (Andrei et al. 2003; Harada et al. 2003; Allu et al. 2010; Boncel et al. 2010) between **37a** and **169a** involving a nucleophilic attack by the enamino double bond (of **169a**) on the electron-deficient double bond (of **37a**), which leads to the formation of **A**. The intramolecular cyclization of **A** involving the attack by the imine nitrogen on the nearby –C(O)Ph moiety affords the spiro-quinoxaline derivative **B**. The rearrangement of the spiro-quinoxalinone **B** is then assumed to occur according to Scheme 6.77, which proceeds by cascade reactions involving: (a) the intramolecular nucleophilic attack by the amino group on the carbonyl group with the intermediate formation of the hydroxy-derivative **C**, (b) the ring-opening with the cleavage of the C(2)–C(3) bond in the hydroxy-derivative **C** with the elimination of water leading to the formation of the final product **170a**.

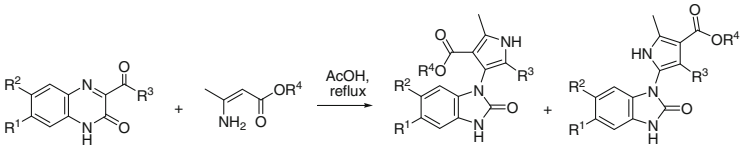
In the case of the formation of *N*-(pyrrol-2-yl)benzimidazol-2-ones **171** at its initial stage there occurs a nucleophilic attack by the enamino double bond (of **169a**) on the electron-deficient benzoyl carbonyl group (of **37a**) which leads to the formation of **D** (Scheme 6.77, *Pathway II*). This brings about the rearrangement product via intermediates **E** and **F**.

With this result at disposal, we went on to study the scope of the methodology, with respect to the 5- and 7-aza- quinoxalin-2(1*H*)-ones, namely 3-benzoylpyrido [3,2-*b*]pyrazin-2(1*H*)-one **95a** and 3-benzoylpyrido[3,4-*b*]pyrazin-2(1*H*)-one **95d** (Scheme 6.78). As can be seen, this chemistry is not limited to the quinoxalin-2 (1*H*)-ones, and the compounds composed of two heterocyclic fragments are acceptable substrates as well (Mamedov et al. 2014e).

The reactions proceed perfectly well with both **95a** and **95d** pyrazin-2(1*H*)-one derivatives, with the formation of the easily separable regioisomeric products **172/173** and **174/175** with overall quantitative yields.

In comparison with the existing methods, the present approach offers the following advantages: (i) it proceeds faster and affords good to excellent yields under mild conditions with no additional activation modes such as microwave irradiation, (ii) it is

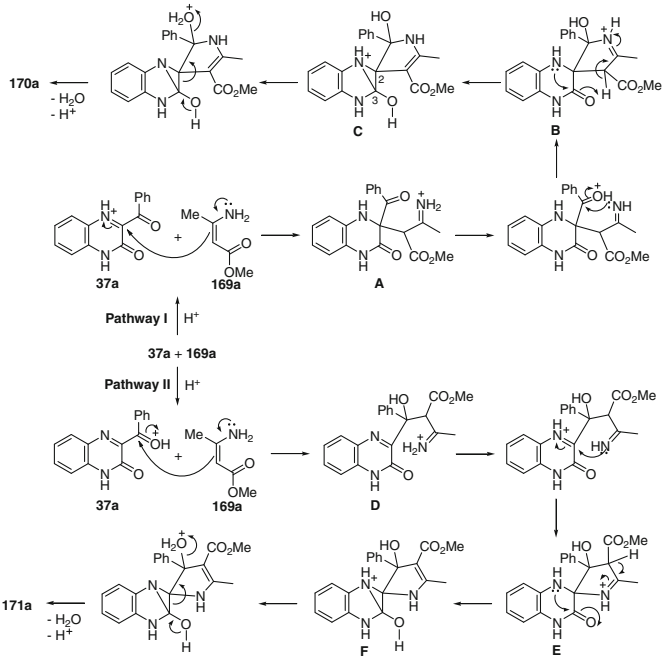
Table 6.20 Synthesis of *N*-pyrrolylbenzimidazol-2-ones **170** and **171**



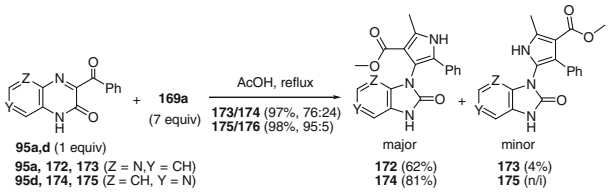
37 (1 equiv) **169** (7 equiv) **170** (major) **171** (minor)

Entry	**37**	R^1	R^2	R^3	**169**	R^4	Products (yield)	Overall yield, (**170**/**171**)[a]
1	**37a**	H	H	Ph	**169a**	Me	**170a** + **171a** (45 %) (n/i)	97 %, 78:22
2	**37b**	H	H	C_6H_4F-4	**169a**	Me	**170b** + **171b** (42 %) (n/i)	94 %, 74:26
3	**37c**	H	H	C_6H_4Cl-4	**169a**	Me	**170c** + **171c** (52 %) (n/i)	97 %, 72:28
4	**37d**	H	H	C_6H_4Br-4	**169a**	Me	**170d** + **171d** (51 %) (n/i)	97 %, 70:30
5	**37e**	H	H	C_6H_4I-4	**169a**	Me	**170e** + **171e** (53 %) (n/i)	98 %, 75:25
6	**37i**	H	H	*n*-Pr	**169a**	Me	**170f** + **171f** (39 %) (n/i)	97 %, 91:9
7	**37x**	Me	Me	Ph	**169a**	Me	**170g** + **171g** (62 %) (n/i)	97 %, 83:17
8	**37t**	COPh	H	Ph	**169a**	Me	**170h** + **171h** (43 %) (n/i)	97 %, 79:21
9	**37a**	H	H	Ph	**169b**	Et	**170i** + **171i** (58 %, 24 %) (4 %)	99 %, 78:22
10	**37b**	H	H	C_6H_4F-4	**169b**	Et	**170j** + **171j** (59 %) (n/i)	96 %, 77:23
11	**37c**	H	H	C_6H_4Cl-4	**169b**	Et	**170k** + **171k** (61 %, 40 %) (5 %)	97 %, 67:33
12	**37d**	H	H	C_6H_4Br-4	**169b**	Et	**170l** + **171l** (56 %, 38 %) (4 %)	99 %, 67:33
13	**37e**	H	H	C_6H_4I-4	**169b**	Et	**170m** + **171m** (56 %) (n/i)	98 %, 60:40
14	**37x**	Me	Me	Ph	**169b**	Et	**170n** + **171n** (65 %) (n/i)	99 %, 84:16
15	**37t**	COPh	H	Ph	**169b**	Et	**170o** + **171o** (41 %) (n/i)	98 %, 72:28
16	**37u**	CO_2H	H	Ph	**169b**	Et	**170p** + **171p** (77 %)	89 %, 75:25 (inseparable mixture)

[a]Ratio determined by the ^{1}H NMR of the crude products



Scheme 6.77 Proposed mechanisms for the formation of **170a** (*Pathway I*–via an initial attack on the C(3) atom of quinoxalin-2(1*H*)-one) and **171a** (*Pathway II*–via an initial attack on the C atom of benzoyl group)



Scheme 6.78 Synthesis of *N*-pyrrolyl-1*H*-imidazo[5,4-*b*]- (**172/173**) and *N*-pyrrolyl-1*H*-imidazo [4,5-*c*]pyridin-2(3*H*)-ones (**174/175**)

very cost-effective and uses the inexpensive easily and commercially available reagents, and (iii) it is applicable to a broader range of substrates, including 3-aroyl (alkanoyl)quinoxalin-2(1*H*)-ones, 3-benzoylpyrido[3,2-*b*]pyrazin-2(1*H*)-one and 3-benzoylpyrido[3,4-*b*]pyrazin-2(1*H*)-one and various enamines.

An effective synthesis strategy via the novel quinoxalin-2(1*H*)-one/benzimidazol-2-one rearrangement that makes possible a rapid access to the *N*-pyrrolylbenzimidazol-2-ones from the readily available 3-aroylquinoxalin-2(1*H*)-ones with various substituents and commercially available enamines (methyl and ethyl 3-aminocrotonates) have been developed. The methodology was found to be general and

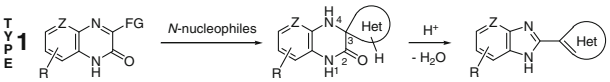
a wide variety of *N*-pyrrolylbenzimidazol-2-one derivatives were prepared in good yields. Due to the availability of the starting materials and the potential applications of the products, this method is highly perspective in organic synthesis and medicinal chemistry. This protocol also represents an extremely simple, efficient and metal-free environmentally friendly way for constructing the substituted pyrroles and benzimidazol-2-ones in overall high yields. Aza-analogues of benzimidazol-2-ones were obtained when aza-analogues of quinoxalin-2(1*H*)-one have been used. Thus it complements the method for the rapid formation of multifunctional heterocycles.

6.11 Conclusion

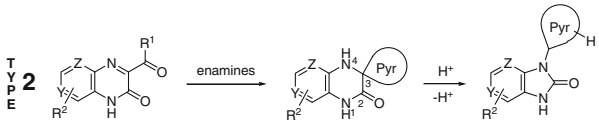
Two fundamentally new rearrangements of quinoxalinones and their aza-analogues have been discovered. The first one can be schematically represented as **TYPE 1** on the Scheme 6.79: "***Any of the spiro-derivatives of 1,2,3,4-tetrahydroquinoxalin-3-one with at least one mobile hydrogen atom in their spiro-forming component are on their way to the benzimidazole derivative with the spiro-forming component at position 2.***"

The second one can be schematically presented as **TYPE 2** on the Scheme 6.80: "***Any of the spiro-derivatives of 1,2,3,4-tetrahydroquinoxalin-3-one without any mobile hydrogen atom in their spiro-forming component are on their way to the benzimidazolone derivative with the spiro-forming component at position 1.***"

Thus, the novel rearrangements presented raises no doubts as to its generality in the synthesis of benzimidazol(on)es. Because in accordance with the aim set both the first and the second component can be replaced when synthesizing any desired derivative of benzimidazole. To date, there were synthesized benzimidazol(on)e derivatives via of these novel rearrangements. These derivatives are shown in the review. We hope that in future these new rearrangements, based on the rearrangement of quinoxalin(on)e derivatives into benzimidazol(on)e derivatives, will find



Scheme 6.79 Schematical presentation of the rearrangement TYPE 1



Scheme 6.80 Schematical presentation of the rearrangement TYPE 2

their worthy place in the chemistry of heterocyclic compounds, and will serve as a simple and efficient method for the synthesis of various benzimidazole derivatives, along with the classical Phillips-Ladenburg and Weidenhagen reactions.

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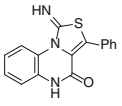
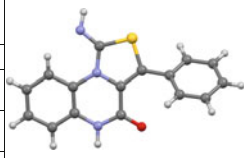
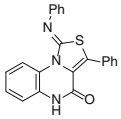
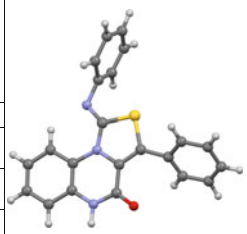
Appendix

The X-structures of some compounds referred to in Chap. 2

MANCEJ	 **508** ($R^1 = R^3 = H$)		Mamedov VA, Kalinin AA, Gubaidullin AT, Nurkhametova IZ, Litvinov IA, Levin YaA (1999) Chem Heterocyclyc Compd 35(12):1459-1473			
Formula	$C_{16}H_{11}N_3OS$					
Compound Name	1-Imino-3-phenyl-4-oxo-4,5-dihydrothiazolo(3,4-*a*)quinoxaline					
Space Group	P-1	***Cell: (Å,°)***	***a*** 11.641(1)	***b*** 13.778(5)	***c*** 18.303(4)	
Space Group No.	2		α 96.69(3)	β 93.53(2)	γ 101.61(2)	
R-Factor (%)	6.60	***Temperature (K):***	295	***Density (g/cm^3):***	1.461	

OBIZIJ	 **508a**		Mamedov VA, Nurkhametova IZ, Gubaidullin AT, Litvinov IA, Tsuboi S (2004) Heterocycles 63(8):1783-1792			
Formula	$C_{22}H_{15}N_3OS$					
Compound Name	1-(Phenylimino)-3-phenyl-4,5-dihydro-1*H*-thiazolo(3,4-*a*)quinoxalin-4-one					
Space Group	P21/n	***Cell: (Å,°)***	***a*** 8.355(2)	***b*** 9.371(4)	***c*** 28.250(40)	
Space Group No.	14		α 90.00	β 93.19(3)	γ 90.00	
R-Factor (%)	5.10	***Temperature (K):***	294	***Density (g/cm^3):***	1.346	

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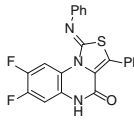
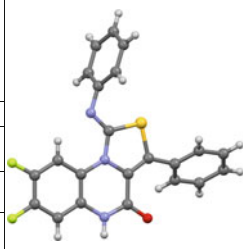
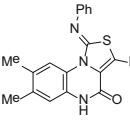
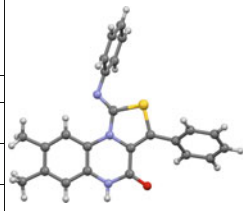
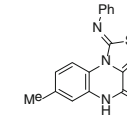
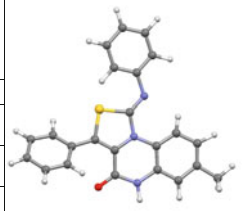
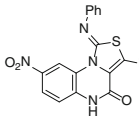
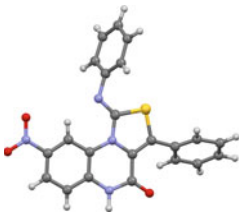
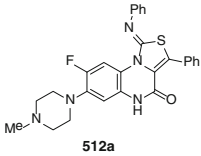
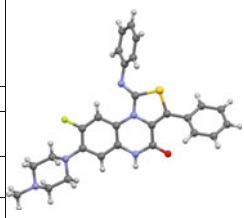
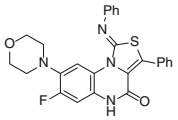
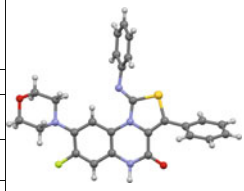
KAMVOK	 **509a**		Mamedov VA, Nurkhametova IZ, Kotovskaya SK, Gubaidullin AT, Levin YaA, Litvinov IA, Charushin VN (2004) Russ Chem Bull, Int Ed 53(11):2568-2576			
Formula	$C_{22}H_{13}F_2N_3OS$					
Compound Name	4,5-Dihydro-7,8-difluoro-3-phenyl-1-(phenylimino)thiazolo(3,4-*a*) quinoxalin-4-one					
Space Group	P21/n	***Cell: (Å,°)***	***a*** 8.823(5)	***b*** 8.962(8)	***c*** 28.587(6)	
Space Group No.	14		α 90.00	β 90.03(2)	γ 90.00	
R-Factor (%)	7.52	***Temperature (K):***	295	***Density (g/cm^3):***	1.421	

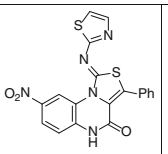
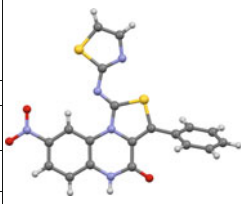
APIDAF	 **509b**		Mamedov VA, Zhukova NA, Beschastnova TN, Gubaidullin AT, Levin YaA, Litvinov IA (2009) Russ Chem Bull, Int Ed 58(1):191-202			
Formula	$C_{24}H_{19}N_3OS$					
Compound Name	7,8-Dimethyl-3-phenyl-1-(phenylimino)[1,3]thiazolo[3,4-*a*]quinoxalin-4(5*H*)-one					
Space Group	P21/n	***Cell: (Å,°)***	***a*** 8.530(1)	***b*** 9.379(1)	***c*** 29.260(6)	
Space Group No.	14		α 90.00	β 91.70(1)	γ 90.00	
R-Factor (%)	7.19	***Temperature (K):***	295	***Density (g/cm^3):***	1.350	

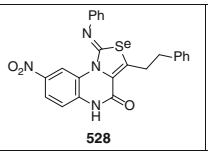
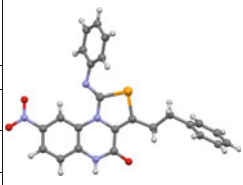
OBIZUV	 **510a**		Gubaidullin AT, Mamedov VA, Litvinov IA (2004) ARKIVOC 5:80-12			
Formula	$C_{23}H_{17}N_3OS$					
Compound Name	1-(Phenylimino)-3-phenyl-7-methyl-4,5-dihydro-1*H*-thiazolo(3,4-*a*)quinoxalin-4-one					
Space Group	P21/c	***Cell: (Å,°)***	***a*** 4.857(7)	***b*** 20.420(10)	***c*** 19.137(6)	
Space Group No.	14		α 90.00	β 96.11(7)	γ 90.00	
R-Factor (%)	5.30	***Temperature (K):***	294	***Density (g/cm^3):***	1.350	

OBIZOP	 **511b**		Mamedov VA, Nurkhametova IZ, Kotovskaya SK, Gubaidullin AT, Levin YaA, Litvinov IA, Charushin VN (2004) Russ Chem Bull, Int Ed 53(11):2568-2576		
Formula	$C_{22}H_{14}N_4O_3S$				
Compound Name	1-(Phenylimino)-3-phenyl-8-nitro-4,5-dihydro-1*H*-thiazolo(3,4-*a*) quinoxalin-4-one				
Space Group	P21/n	***Cell: (Å,°)***	***a*** 9.602(2)	***b*** 8.781(3)	***c*** 28.069(4)
Space Group No.	14		α 90.00	β 92.64(1)	γ 90.00
R-Factor (%)	4.60	***Temperature (K):***	294	***Density (g/cm^3):***	1.370

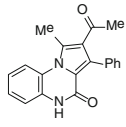
UKUTUQ	 **512a**		Mamedov VA, Zhukova NA, Beschastnova TN, Balandina AA, Gubaidullin AT, Kotovskaya SK, Latypov ShK, Levin YaA, Charushin VN (2009) Russ Chem Bull, Int Ed 58(1):203-211		
Formula	$C_{27}H_{24}FN_5OS$				
Compound Name	8-Fluoro-7-(4-methylpiperazin-1-yl)-3-phenyl-1-(phenylimino)[1, 3]thiazolo[3,4-*a*]quinoxalin-4(5*H*)-one				
Space Group	P-1	***Cell: (Å,°)***	***a*** 8.586(2)	***b*** 12.083(7)	***c*** 13.819(5)
Space Group No.	2		α 99.19(4)	β 91.24(4)	γ 96.94(3)
R-Factor (%)	6.82	***Temperature (K):***	295	***Density (g/cm^3):***	1.334

UKUVAY	 **513b**		Mamedov VA, Zhukova NA, Beschastnova TN, Balandina AA, Gubaidullin AT, Kotovskaya SK, Latypov ShK, Levin YaA, Charushin VN (2009) Russ Chem Bull, Int Ed 58(1):203-211		
Formula	$C_{26}H_{21}FN_4O_2S$				
Compound Name	7-Fluoro-8-(morpholin-4-yl)-3-phenyl-1-(phenylimino)[1,3]thiazolo[3,4-*a*]quinoxalin-4(5*H*)-one				
Space Group	P21/n	***Cell: (Å,°)***	***a*** 16.619(2)	***b*** 9.875(0)	***c*** 17.711(2)
Space Group No.	14		α 90.00	β 109.81(0)	γ 90.00
R-Factor (%)	5.27	***Temperature (K):***	293	***Density (g/cm^3):***	1.338

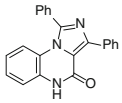
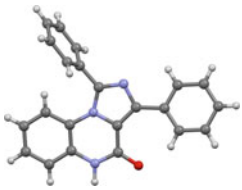
APIDEJ	 **516b**		Mamedov VA, Zhukova NA, Beschastnova TN, Gubaidullin AT, Levin YaA, Litvinov IA (2009) Russ Chem Bull, Int Ed 58(1):191-202		
Formula	$C_{19}H_{11}N_5O_3S_2$				
Compound Name	8-Nitro-3-phenyl-1-(1,3-thiazol-2-ylimino)[1,3]thiazolo[3,4-*a*]quinoxalin-4(5*H*)-one				
Space Group	P-1	***Cell: (Å,°)***	***a*** 7.016(0)	***b*** 12.718(1)	***c*** 13.772(1)
Space Group No.	2		α 72.28(0)	β 87.25(0)	γ 73.64(0)
R-Factor (%)	4.36	***Temperature (K):***	295	***Density (g/cm^3):***	1.464

OPINAD	 **528**		Mamedov VA, Zhukova NA, Gubaidullin AT, Beschastnova TN, Rizvanov IKh, Levin YaA, Litvinov IA (2009) Russ Chem Bull, Int Ed 58(6):1294-1302		
Formula	$C_{24}H_{18}N_4O_3Se$				
Compound Name	8-Nitro-3-(2-phenylethyl)-1-phenylimino-[1,3]selenazolo[3,4-*a*]quinoxalin-4(5*H*)-one				
Space Group	P21/n	***Cell: (Å,°)***	***a*** 15.306(1)	***b*** 8.060(0)	***c*** 20.663(1)
Space Group No.	14		α 90.00	β 90.75(0)	γ 90.00
R-Factor (%)	4.00	***Temperature (K):***	295	***Density (g/cm^3):***	1.466

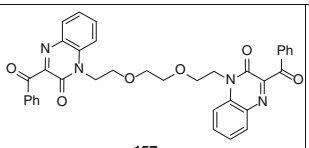
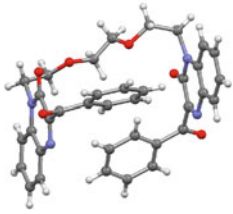
The X-structures of some compounds referred to Chap. 3

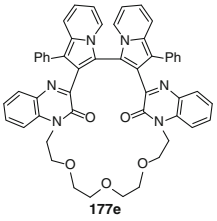
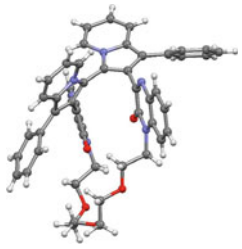
AZEJIY	 **25a**		Mamedov VA, Kalinin AA, Gubaidullin AT, Litvinov IA, Azancheev NM, Levin YaA (2004) Russ J Org Chem 40(1):114-123		
Formula	$C_{20}H_{16}N_2O_2$				
Compound Name	2-Acetyl-1-methyl-4-oxo-3-phenyl-4,5-dihydropyrrolo(1,2-*a*)quinoxaline				
Space Group	P21/a	***Cell: (Å,°)***	***a*** 6.784(3)	***b*** 29.880(20)	***c*** 8.379(4)
Space Group No.	14		α 90.00	β 108.21(4)	γ 90.00
R-Factor (%)	5.10	***Temperature (K):***	295	***Density (g/cm^3):***	1.302

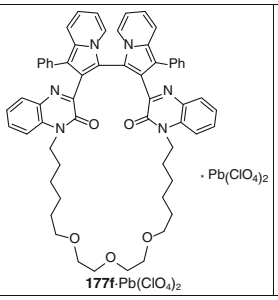
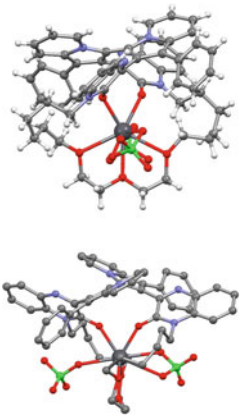
The X-structures of some compounds referred to Chap. 4

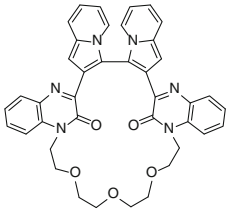
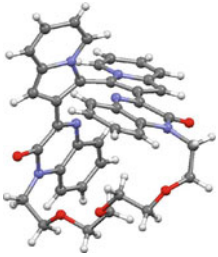
IWOMOX	 **12a**	Mamedov VA, Zhukova NA, Beschastnova TN, Gubaidullin AT, Rakov DV, Rizvanov IKh (2011) Tetrahedron Lett. 52:4280-4284			
Formula	$C_{22}H_{15}N_3O$				
Compound Name	1,3-Diphenylimidazo[1,5-*a*]quinoxalin-4(5*H*)-one				
Space Group	P21/c	***Cell: (Å,°)***	***a*** 15.074(5)	***b*** 5.078(1)	***c*** 23.490(8)
Space Group No.	14		α 90.00	β 107.79(0)	γ 90.00
R-Factor (%)	7.31	***Temperature (K):***	296	***Density (g/cm^3):***	1.309

The X-structures of some compounds referred to in Chap. 5

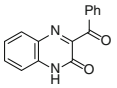
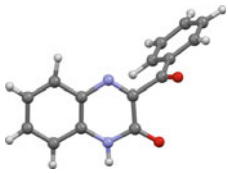
QIXCUW	 **157a**	Mamedov VA, Kalinin AA, Gubaidullin AT, Gorbunova EA, Litvinov IA (2006) Russ J Org Chem 42(10):1532-1543			
Formula	$C_{36}H_{30}N_4O_6$				
Compound Name	1,8-bis(3-Benzoylquinoxalin-2-one-1-yl)-3,6-dioxaoctane				
Space Group	P21/a	***Cell: (Å,°)***	***a*** 11.930(20)	***b*** 23.710(10)	***c*** 12.090(20)
Space Group No.	14		α 90.00	β 117.40(10)	γ 90.00
R-Factor (%)	7.09	***Temperature (K):***	295	***Density (g/cm^3):***	1.345

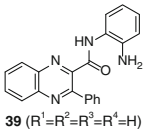
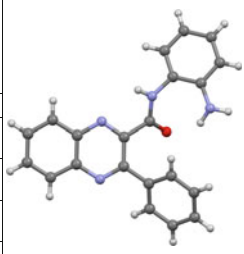
RODCUJ	 **177e**	Mamedov VA, Kalinin AA, Yanilkin VV, Nastapova NV, Morozov VI, Balandina AA, Gubaidullin AT, Isaikina OG, Chernova AV, Latypov ShK, Litvinov IA (2007) Russ Chem Bull, Int Ed 56(10):2060-2071			
Formula	$C_{25}H_{42}N_6O_5$				
Compound Name	$2^1,3^1$-Diphenyl-$1^2,4^2$-dioxo-7,10,13-trioxa-1,4(3,1)-diquinoxalino-2(2,3), 3(3,2)-diindolizinocyclopentadecaphane				
Space Group	P21/n	***Cell: (Å,°)***	***a*** 13.028(5)	***b*** 24.559(5)	***c*** 16.374(4)
Space Group No.	14		α 90.00	β 103.28(2)	γ 90.00
R-Factor (%)	7.30	***Temperature (K):***	295	***Density (g/cm^3):***	1.273

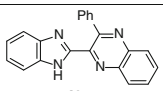
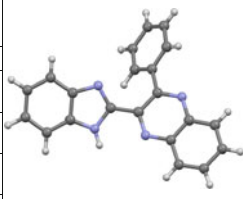
KITGIF	 **177f**·$Pb(ClO_4)_2$		Mamedov VA, Kalinin AA, Gubaidullin AT, Katsuba SA, Syakaev VV, Rizvanov IK, Latypov SK (2013) Tetrahedron 69:10675-10687		
Formula	$C_{60}H_{58}N_6O_5 \bullet Pb(ClO_4)_2$				
Compound Name	(3,18-Diphenyl-35,38,41-trioxa-9,12,21,28,48,55-hexaazanonacyclo[46.7.1.1^{20,28}.0^{2,10}.0^{4,9}.0^{11,19}.0^{12,17}.0^{22,27}.0^{49,54}]heptapentaconta-1(55),2(10),3,5,7,11(19),13,15,17,20,22,24,26,49,51,53-hexadecaene-56,57-dione)-(perchlorato-O,O')-(perchlorato-O)-lead				
Space Group	P21/n	***Cell: (Å,°)***	***a*** 16.943(6)	***b*** 17.939(7)	***c*** 22.611(9)
Space Group No.	14		α 90.00	β 99.75(0)	γ 90.00
R-Factor (%)	5.69	***Temperature (K):***	296	***Density (g/cm^3):***	1.557

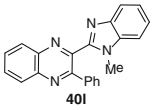
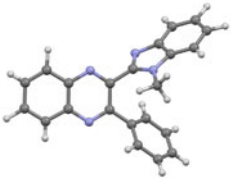
GILREA	 **177m**		Mamedov VA, Kalinin AA, Samigullina AI, Mironova EV, Krivolapov DB, Gubaidullin AT, Rizvanov IK (2013) Tetrahedron Lett 54:3348-3352		
Formula	$C_{40}H_{34}N_6O_5$				
Compound Name	31,34,37-Trioxa-9,12,21,28,40,47-hexaazanonacyclo[38.7.1.1^{20,28}.0^{2,10}.0^{4,9}.0^{11,19}.0^{12,17}.0^{22,27}.0^{41,46}]nonatetraconta-1(47),2(10),3,5,7,11(19),13,15,17,20,22,24,26,41,43,45-hexadecaene-48,49-dione				
Space Group	P21/n	***Cell: (Å,°)***	***a*** 14.999(3)	***b*** 15.213(3)	***c*** 15.854(4)
Space Group No.	14		α 90.00	β 112.99(0)	γ 90.00
R-Factor (%)	5.78	***Temperature (K):***	150	***Density (g/cm^3):***	1.354

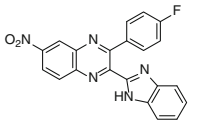
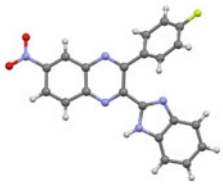
The X-structures of some compounds referred to in Chap. 6

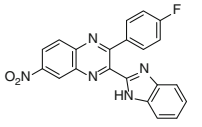
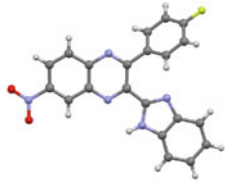
TAKLIB	 **37a**		Mamedov VA, Kalinin AA, Gubaidullin AT, Litvinov IA, Levin YaA (2002) Chem Heterocyclic Compd 38(12):1504-1510			
Formula	$C_{15}H_{10}N_2O_2$					
Compound Name	3-Benzoyl-2-oxo-1,2-dihydroquinoxaline					
Space Group	P21/n	***Cell: (Å,°)***	***a*** 14.470(20)	***b*** 5.604(2)	***c*** 15.090(10)	
Space Group No.	14		α 90.00	β 105.02(7)	γ 90.00	
R-Factor (%)	4.90	***Temperature (K):***	295	***Density (g/cm^3):***	1.406	

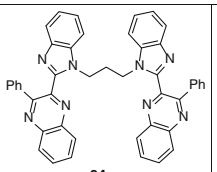
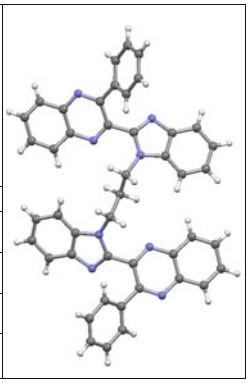
USOTOM	 **39** (R^1=R^2=R^3=R^4=H)		Mamedov VA, Zhukova NA, Beschastnova TN, Gubaidullin AT, Balandina AA, Latypov SK (2010) Tetrahedron 66:9745-9753			
Formula	$C_{21}H_{16}N_4O$					
Compound Name	N-(2-Aminophenyl)-3-phenylquinoxaline-2-carboxamide					
Space Group	P21/c	***Cell: (Å,°)***	***a*** 30.468(3)	***b*** 12.677(1)	***c*** 9.015(0)	
Space Group No.	14		α 90.00	β 97.08(0)	γ 90.00	
R-Factor (%)	4.64	***Temperature (K):***	296	***Density (g/cm^3):***	1.309	

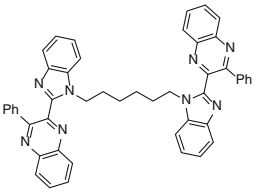
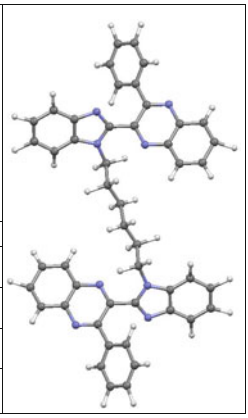
AZEHUI	 **40a**		Mamedov VA, Kalinin AA, Gubaidullin AT, Chernova AV, Litvinov IA, Levin YaA, Shagidullin RR (2004) Russ Chem Bull, Int Ed 53(1):164-175			
Formula	$C_{21}H_{14}N_4$					
Compound Name	2-(Benzimidazol-2-yl)-3-phenylquinoxaline					
Space Group	P21/n	***Cell: (Å,°)***	***a*** 8.181(3)	***b*** 20.494(5)	***c*** 10.364(4)	
Space Group No.	14		α 90.00	β 112.77(3)	γ 90.00	
R-Factor (%)	4.00	***Temperature (K):***	295	***Density (g/cm^3):***	1.336	

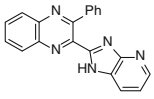
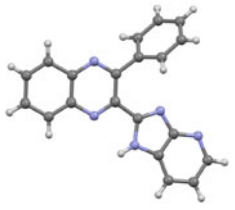
AZEJAQ	 **40l**		Mamedov VA, Kalinin AA, Gubaidullin AT, Chernova AV, Litvinov IA, Levin YaA, Shagidullin RR (2004) Russ Chem Bull, Int Ed 53(1):164-175			
Formula	$C_{22}H_{16}N_4$					
Compound Name	2-(1-Methylbenzimidazol-2-yl)-3-phenylquinoxaline					
Space Group	P-1	***Cell: (Å,°)***	***a*** 6.389(1)	***b*** 11.697(4)	***c*** 12.621(6)	
Space Group No.	2		α 71.19(4)	β 89.86(3)	γ 77.18(2)	
R-Factor (%)	4.20	***Temperature (K):***	295	***Density (g/cm^3):***	1.287	

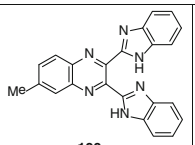
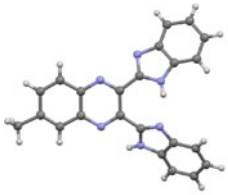
USOTUS	 **91d**		Mamedov VA, Zhukova NA, Beschastnova TN, Gubaidullin AT, Balandina AA, Latypov SK (2010) Tetrahedron 66:9745-9753			
Formula	$C_{21}H_{12}FN_5O_2$					
Compound Name	2-(1*H*-Benzimidazol-2-yl)-3-(4-fluorophenyl)-6-nitroquinoxaline					
Space Group	Pna21	***Cell: (Å,°)***	***a*** 34.968(14)	***b*** 12.356(5)	***c*** 4.004(1)	
Space Group No.	33		α 90.00	β 90.00	γ 90.00	
R-Factor (%)	5.06	***Temperature (K):***	296	***Density (g/cm^3):***	1.479	

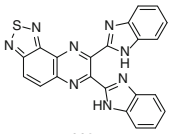
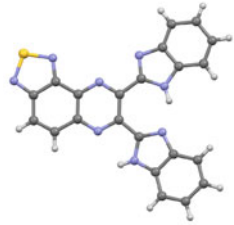
USOTEC	 **92d**		Mamedov VA, Zhukova NA, Beschastnova TN, Gubaidullin AT, Balandina AA, Latypov SK (2010) Tetrahedron 66:9745-9753			
Formula	$C_{21}H_{12}FN_5O_2$					
Compound Name	3-(1*H*-Benzimidazol-2-yl)-2-(4-fluorophenyl)-6-nitroquinoxaline					
Space Group	Pbca	***Cell: (Å,°)***	***a*** 6.960(0)	***b*** 23.182(3)	***c*** 24.896(3)	
Space Group No.	61		α 90.00	β 90.00	γ 90.00	
R-Factor (%)	4.92	***Temperature (K):***	296	***Density (g/cm^3):***	1.473	

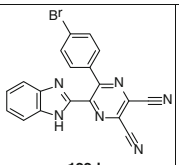
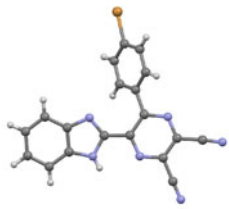
QIXDAD	 **94c**		Mamedov VA, Kalinin AA, Gubaidullin AT, Gorbunova EA, Litvinov IA (2006) Russ J Org Chem 42(10):1532-1543			
Formula	$C_{45}H_{32}N_8$					
Compound Name	1,3-bis(2-(3-Phenylquinoxalin-2-yl)benzimidazol-1-yl)propane					
Space Group	I2/a	***Cell: (Å,°)***	***a*** 15.170(20)	***b*** 13.440(20)	***c*** 20.430(20)	
Space Group No.	15		α 90.00	β 103.83(9)	γ 90.00	
R-Factor (%)	11.32	***Temperature (K):***	295	***Density (g/cm³):***	1.276	

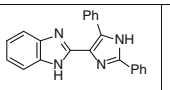
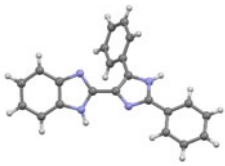
QIXDEH	 **94d**		Mamedov VA, Kalinin AA, Gubaidullin AT, Gorbunova EA, Litvinov IA (2006) Russ J Org Chem 42(10):1532-1543			
Formula	$C_{48}H_{38}N_8$					
Compound Name	1,6-bis(2-(3-Phenylquinoxalin-2-yl)benzimidazol-1-yl)hexane					
Space Group	P21/n	***Cell: (Å,°)***	***a*** 11.014(0)	***b*** 8.924(6)	***c*** 20.400(20)	
Space Group No.	14		α 90.00	β 101.92(2)	γ 90.00	
R-Factor (%)	6.10	***Temperature (K):***	295	***Density (g/cm³):***	1.231	

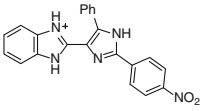
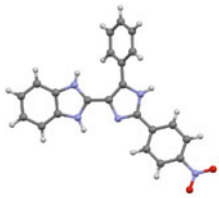
USOTIG	 **96a**		Mamedov VA, Zhukova NA, Beschastnova TN, Gubaidullin AT, Balandina AA, Latypov SK (2010) Tetrahedron 66:9745-9753			
Formula	$C_{20}H_{13}N_5$					
Compound Name	2-(1*H*-Imidazo[4,5-*b*]pyridin-2-yl)-3-phenylquinoxaline					
Space Group	P-1	***Cell: (Å,°)***	***a*** 5.759(1)	***b*** 12.443(2)	***c*** 15.192(3)	
Space Group No.	2		α 67.36(1)	β 84.87(1)	γ 86.16(1)	
R-Factor (%)	5.95	***Temperature (K):***	296	***Density (g/cm³):***	1.193	

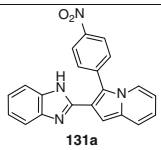
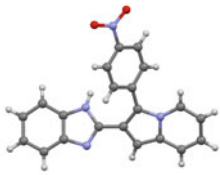
KETPUW	 **100c**		Mamedov VA, Zhukova NA, Syakaev VV, Gubaidullin AT, Beschastnova TN, Adgamova DI, Samigullina AI, Latypov SK (2013) Tetrahedron 69:1403-1416			
Formula	$C_{23}H_{16}N_6$					
Compound Name	2,3-bis(1*H*-benzimidazol-2-yl)-6-methylquinoxaline					
Space Group	P-1	***Cell: (Å,°)***	***a*** 9.290(3)	***b*** 9.711(5)	***c*** 11.707(6)	
Space Group No.	2		α 102.41(4)	β 96.64(3)	γ 114.09(3)	
R-Factor (%)	9.26	***Temperature (K):***	150	***Density (g/cm^3):***	1.364	

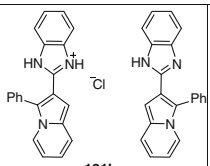
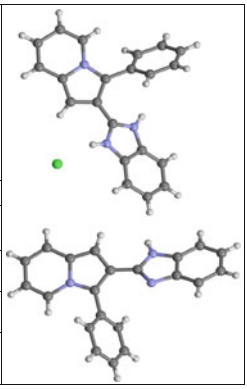
KETPIK	 **119**		Mamedov VA, Zhukova NA, Syakaev VV, Gubaidullin AT, Beschastnova TN, Adgamova DI, Samigullina AI, Latypov SK (2013) Tetrahedron 69:1403-1416			
Formula	$C_{22}H_{12}N_8S$					
Compound Name	7,8-bis(1*H*-benzimidazol-2-yl)[1,2,5]thiadiazolo[3,4-*f*]quinoxaline					
Space Group	C2/c	***Cell: (Å,°)***	***a*** 27.215(7)	***b*** 8.029(2)	***c*** 23.457(6)	
Space Group No.	15		α 90.00	β 118.28(0)	γ 90.00	
R-Factor (%)	7.85	***Temperature (K):***	150	***Density (g/cm^3):***	1.453	

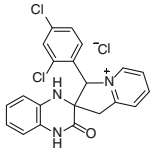
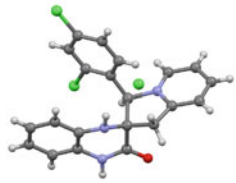
NAQKIB	 **122d**		Mamedov VA, Zhukova NA, Beschastnova TN, Zakirova EI, Kadyrova SF, Mironova EV, Nikonova AG, Latypov SK, Litvinov IA (2012) Tetrahedron Lett 53:292-296			
Formula	$C_{19}H_9BrN_6$					
Compound Name	5-(1*H*-Benzimidazol-2-yl)-6-(4-bromophenyl)pyrazine-2,3-dicarbonitrile					
Space Group	P-1	***Cell: (Å,°)***	***a*** 8.639(1)	***b*** 11.695(2)	***c*** 12.595(3)	
Space Group No.	2		α 84.92(0)	β 88.87(0)	γ 69.39(0)	
R-Factor (%)	5.19	***Temperature (K):***	293	***Density (g/cm^3):***	1.460	

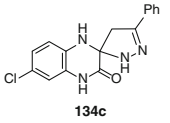
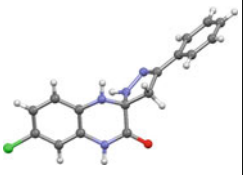
IWOMUD	 **129a**		Mamedov VA, Zhukova NA, Beschastnova TN, Gubaidullin AT, Rakov DV, Rizvanov IKh (2011) Tetrahedron Lett 52:4280-4284			
Formula	$C_{22}H_{16}N_4$					
Compound Name	2-(2,5-diphenyl-1*H*-imidazol-4-yl)-1*H*-benzimidazole					
Space Group	P2121 21	***Cell: (Å,°)***	***a*** 7.884(0)	***b*** 13.379(0)	***c*** 20.117(1)	
Space Group No.	19		α 90.00	β 90.00	γ 90.00	
R-Factor (%)	4.19	***Temperature (K):***	296	***Density (g/cm^3):***	1.297	

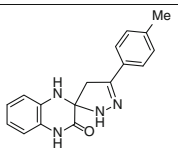
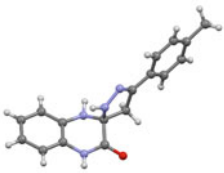
GEJQAP	 **129b**		Mamedov VA, Zhukova NA, Beschastnova TN, Gubaidullin AT (2011) Russ Chem Bull, Int Ed 60(5):933-936			
Formula	$C_{22}H_{16}N_5O_2$					
Compound Name	2-(2-(4-Nitrophenyl)-5-phenyl-1H-imidazol-4-yl)-1*H*-benzimidazol-3-ium					
Space Group	P21/n	***Cell: (Å,°)***	***a*** 8.075(2)	***b*** 21.991(5)	***c*** 15.788(3)	
Space Group No.	14		α 90.00	β 101.08(0)	γ 90.00	
R-Factor (%)	4.21	***Temperature (K):***	295	***Density (g/cm^3):***	1.356	

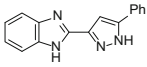
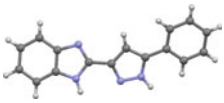
POJHOM	 **131a**		Mamedov VA, Saifina DF, Gubaidullin AT, Saifina AF, Rizvanov IKh (2008) Tetrahedron Lett 49:6231-6233			
Formula	$C_{21}H_{14}N_4O_2$					
Compound Name	2-(3-(4-Nitrophenyl)indolinzin-2-yl)benzimidazole					
Space Group	P21	***Cell: (Å,°)***	***a*** 10.892(1)	***b*** 15.042(2)	***c*** 11.751(2)	
Space Group No.	4		α 90.00	β 117.48(0)	γ 90.00	
R-Factor (%)	8.84	***Temperature (K):***	296	***Density (g/cm^3):***	1.378	

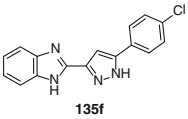
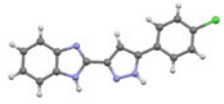
OPIKAA	 **131b**		Mamedov VA, Saifina DF, Gubaidullin AT, Safina AF, Rizvanov IKh, Ganieva VR (2009) Russ Chem Bull, Int Ed 58(9):1986-1990			
Formula	$C_{21}H_{16}N_3Cl$ $C_{21}H_{15}N_3$					
Compound Name	2-(3-Phenylindolizin-2-yl)-1*H*-benzimidazol-3-ium chloride 2-(3-phenylindolizin-2-yl)-1*H*-benzimidazole					
Space Group	P21	***Cell: (Å,°)***	***a*** 10.362(0)	***b*** 16.436(1)	***c*** 11.174(0)	
Space Group No.	4		α 90.00	β 117.63(0)	γ 90.00	
R-Factor (%)	5.43	***Temperature (K):***	295	***Density (g/cm^3):***	1.291	

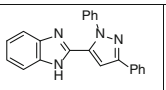
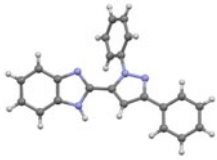
POJHUS	 **132c**		Mamedov VA, Saifina DF, Gubaidullin AT, Saifina AF, Rizvanov IKh (2008) Tetrahedron Lett 49:6231-6233			
Formula	$C_{21}H_{16}Cl_3N_3O$					
Compound Name	3-(2,4-dichlorophenyl)-pentahydrospiro(quinoxalin-2,2'-indolizin)-3(4*H*)-one chloride					
Space Group	P-1	***Cell: (Å,°)***	***a*** 7.435(1)	***b*** 17.032(3)	***c*** 17.361(3)	
Space Group No.	2		α 102.78(0)	β 93.24(0)	γ 98.98(0)	
R-Factor (%)	4.59	***Temperature (K):***	293	***Density (g/cm^3):***	1.458	

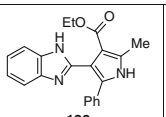
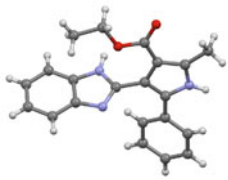
APIVEB	 **134c**		Mamedov VA, Murtazina AM, Gubaidullin AT, Khafizova EA, Rizvanov IKh, Litvinov IA (2010) Russ. Chem. Bull, Int Ed 59(8):1645-1655			
Formula	$C_{16}H_{13}ClN_4O$					
Compound Name	6'-Chloro-5-phenyl-1',2,4,4'-tetrahydro-3'*H*-spiro[pyrazole-3,2'-quinoxalin]-3'-one					
Space Group	P2121 21	***Cell: (Å,°)***	***a*** 5.375(0)	***b*** 9.604(1)	***c*** 28.390(4)	
Space Group No.	19		α 90.00	β 90.00	γ 90.00	
R-Factor (%)	5.08	***Temperature (K):***	295	***Density (g/cm^3):***	1.418	

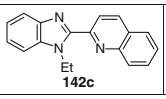
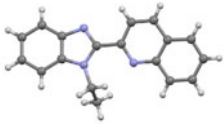
NUGWAO	 **134e**		Mamedov VA, Murtazina AM, Gubaidullin AT, Hafizova EA, Rizvanov IKh (2009) Tetrahedron Lett 50:5186-5189			
Formula	$C_{17}H_{16}N_4O$					
Compound Name	5-(4-Methylphenyl)-1',2,4,4'-tetrahydro-3'*H*-spiro[pyrazole-3,2'-quinoxalin]-3'-one					
Space Group	P2121 21	***Cell: (Å,°)***	***a*** 5.609(3)	***b*** 9.854(5)	***c*** 27.272(15)	
Space Group No.	19		α 90.00	β 90.00	γ 90.00	
R-Factor (%)	3.52	***Temperature (K):***	296	***Density (g/cm^3):***	1.288	

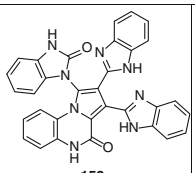
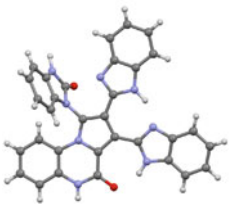
NUGVUH	 **135a**		Mamedov VA, Murtazina AM, Gubaidullin AT, Hafizova EA, Rizvanov IKh (2009) Tetrahedron Lett 50:5186-5189			
Formula	$C_{16}H_{12}N_4$					
Compound Name	2-(5-Phenyl-1*H*-pyrazol-3-yl)-1*H*-benzimidazole					
Space Group	P21/n	***Cell: (Å,°)***	***a*** 7.184(0)	***b*** 14.895(0)	***c*** 18.233(1)	
Space Group No.	14		α 90.00	β 92.50(0)	γ 90.00	
R-Factor (%)	5.17	***Temperature (K):***	296	***Density (g/cm^3):***	1.296	

APIVIF	 **135f**		Mamedov VA, Murtazina AM, Gubaidullin AT, Khafizova EA, Rizvanov IKh, Litvinov IA (2010) Russ. Chem. Bull, Int Ed 59(8):1645-1655			
Formula	$C_{16}H_{11}ClN_4$					
Compound Name	2-(5-(4-Chlorophenyl)-1*H*-pyrazol-3-yl)-1*H*-benzimidazole					
Space Group	P21/n	***Cell: (Å,°)***	***a*** 7.201(5)	***b*** 18.339(13)	***c*** 15.269(11)	
Space Group No.	14		α 90.00	β 92.64(1)	γ 90.00	
R-Factor (%)	7.11	***Temperature (K):***	295	***Density (g/cm^3):***	1.368	

APIVOL	 **137a**		Mamedov VA, Murtazina AM, Gubaidullin AT, Khafizova EA, Rizvanov IKh, Litvinov IA (2010) Russ. Chem. Bull, Int Ed 59(8):1645-1655			
Formula	$C_{22}H_{16}N_4$					
Compound Name	2-(1,3-Diphenyl-1*H*-pyrazol-5-yl)-1*H*-benzimidazole					
Space Group	I41/a	***Cell: (Å,°)***	***a*** 22.002(1)	***b*** 22.002(1)	***c*** 14.911(0)	
Space Group No.	88		α 90.00	β 90.00	γ 90.00	
R-Factor (%)	4.32	***Temperature (K):***	296	***Density (g/cm^3):***	1.238	

BAFHIB	 **139**		Mamedov VA, Khafizova EA, Gubaidullin AT, Murtazina AM, Adgamova DI, Samigullina AI, I.A. Litvinov IA (2011) Russ. Chem. Bull, Int Ed 60(2):368-372			
Formula	$C_{21}H_{19}N_3O_2$					
Compound Name	Ethyl 4-(1*H*-benzimidazol-2-yl)-2-methyl-5-phenyl-1*H*-pyrrole-3-carboxylate					
Space Group	P-1	***Cell: (Å,°)***	***a*** 9.526(1)	***b*** 10.954(1)	***c*** 11.833(2)	
Space Group No.	2		α 111.56(0)	β 94.15(0)	γ 105.14(0)	
R-Factor (%)	5.30	***Temperature (K):***	295	***Density (g/cm^3):***	1.151	

MACNOV	 **142c**		Mamedov VA, Saifina DF, Gubaidullin AT, Ganieva VR, Kadyrova SF, Rakov DV, Rizvanov IKh, Sinyashin OG (2010) Tetrahedron Lett 51:6503-6506			
Formula	$C_{18}H_{15}N_3$					
Compound Name	2-(1-Ethyl-1*H*-benzimidazol-2-yl)quinoline					
Space Group	Pca21	***Cell: (Å,°)***	***a*** 21.506(2)	***b*** 4.963(0)	***c*** 13.158(1)	
Space Group No.	29		α 90.00	β 90.00	γ 90.00	
R-Factor (%)	5.46	***Temperature (K):***	296	***Density (g/cm^3):***	1.293	

KETPOQ	 **159**		Mamedov VA, Zhukova NA, Syakaev VV, Gubaidullin AT, Beschastnova TN, Adgamova DI, Samigullina AI, Latypov SK (2013) Tetrahedron 69:1403-1416		
Formula	$C_{32}H_{20}N_8O_2$				
Compound Name	2,3-bis(1*H*-benzimidazol-2-yl)-1-(2-oxo-2,3-dihydro-1*H*-benzimidazol-1-yl)pyrrolo[1,2-*a*]quinoxalin-4(5*H*)-one				
Space Group	P21/c	***Cell: (Å,°)***	***a*** 18.943(10)	***b*** 13.840(8)	***c*** 14.597(8)
Space Group No.	14		α 90.00	β 102.02(0)	γ 90.00
R-Factor (%)	7.25	***Temperature (K):***	150	***Density (g/cm^3):***	1.363