

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), antihelminthic (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

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 (Kato 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.

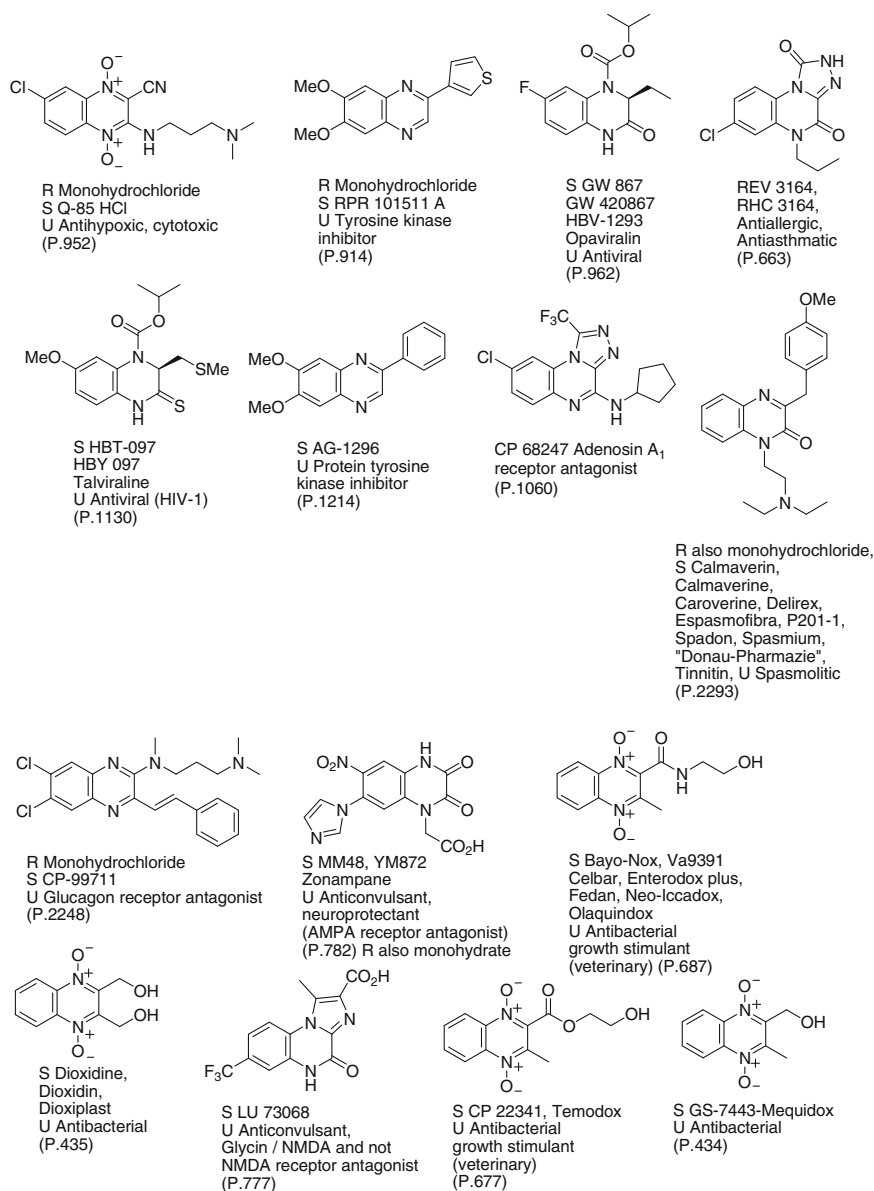


Fig. 2.1 Quinoxaline containing drugs and their synonyms

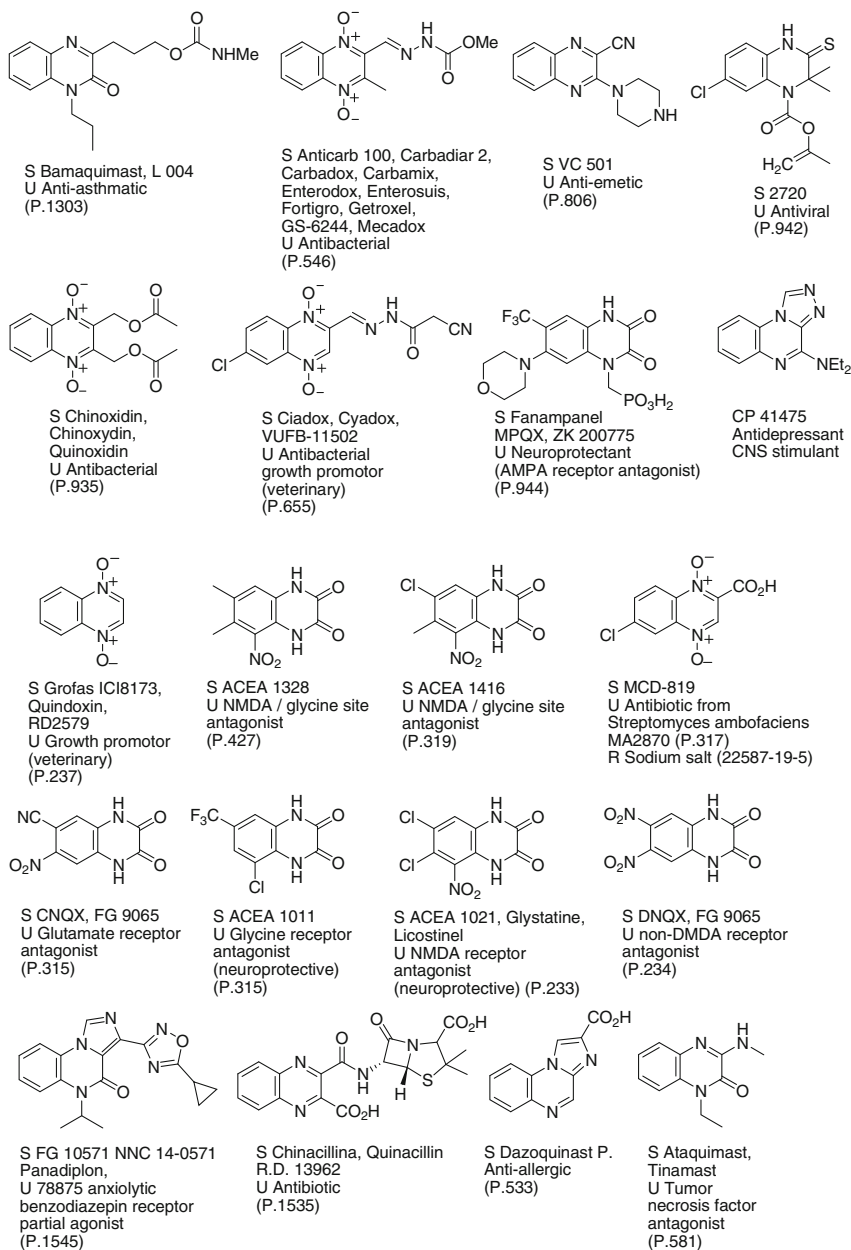


Fig. 2.1 (continued)

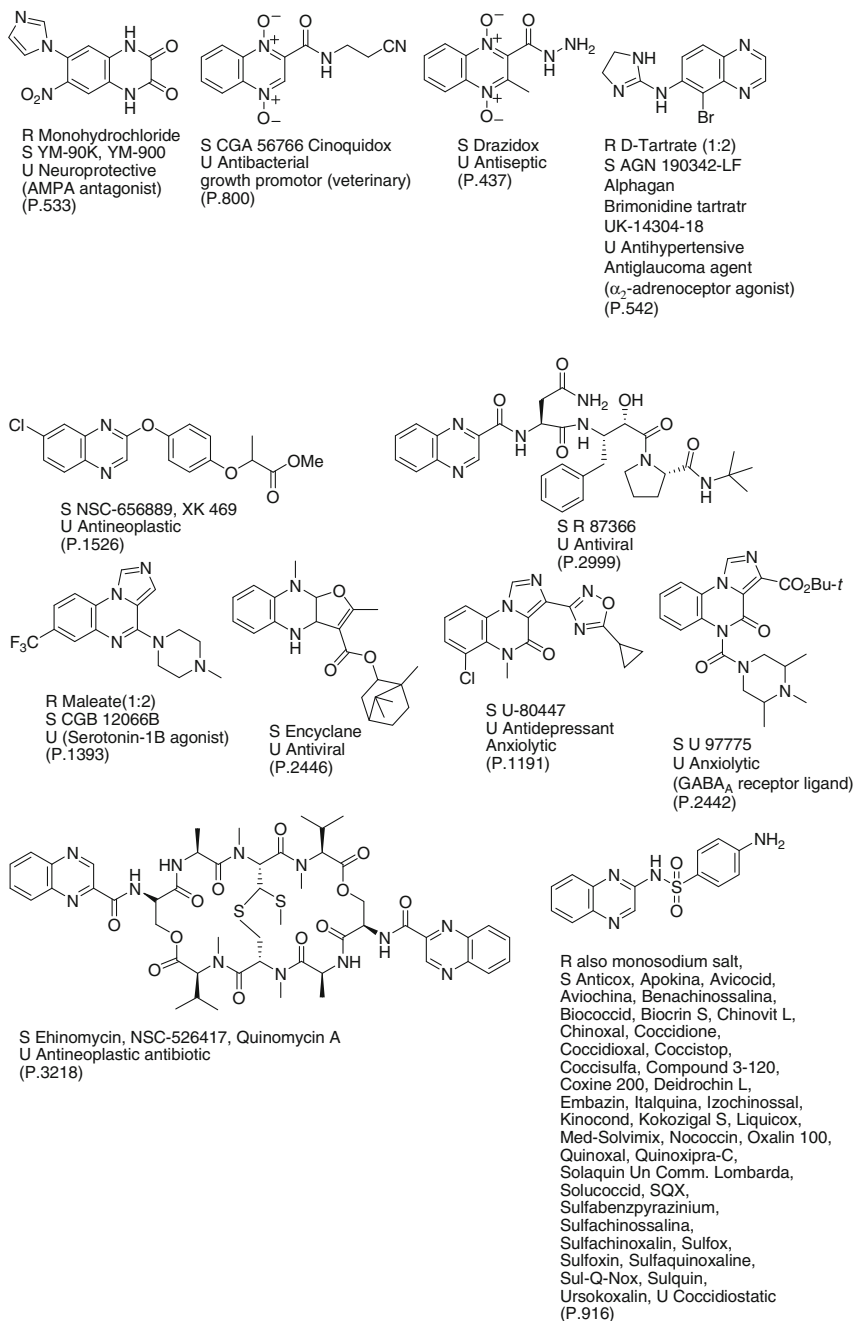


Fig. 2.1 (continued)

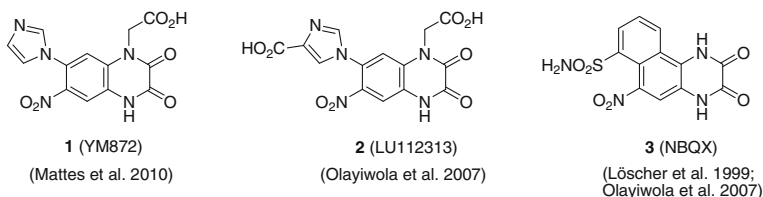


Fig. 2.2 Antibiotic and AMPA receptor antagonists containing quinoxaline core structures

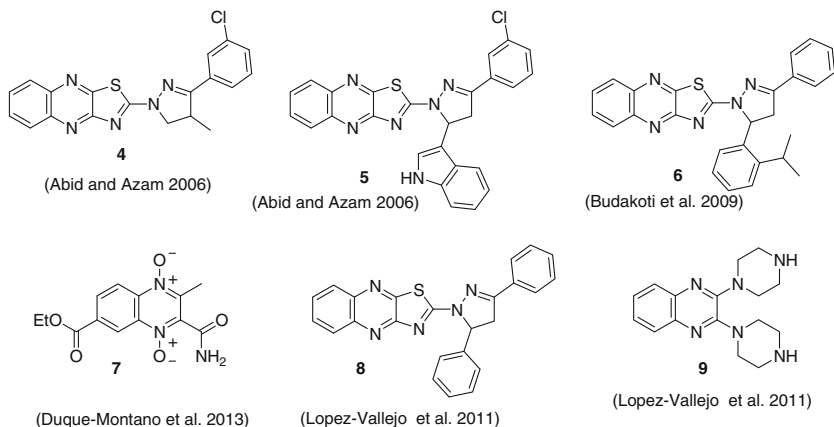


Fig. 2.3 Some quinoxaline motifs with antiamebic activity

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.

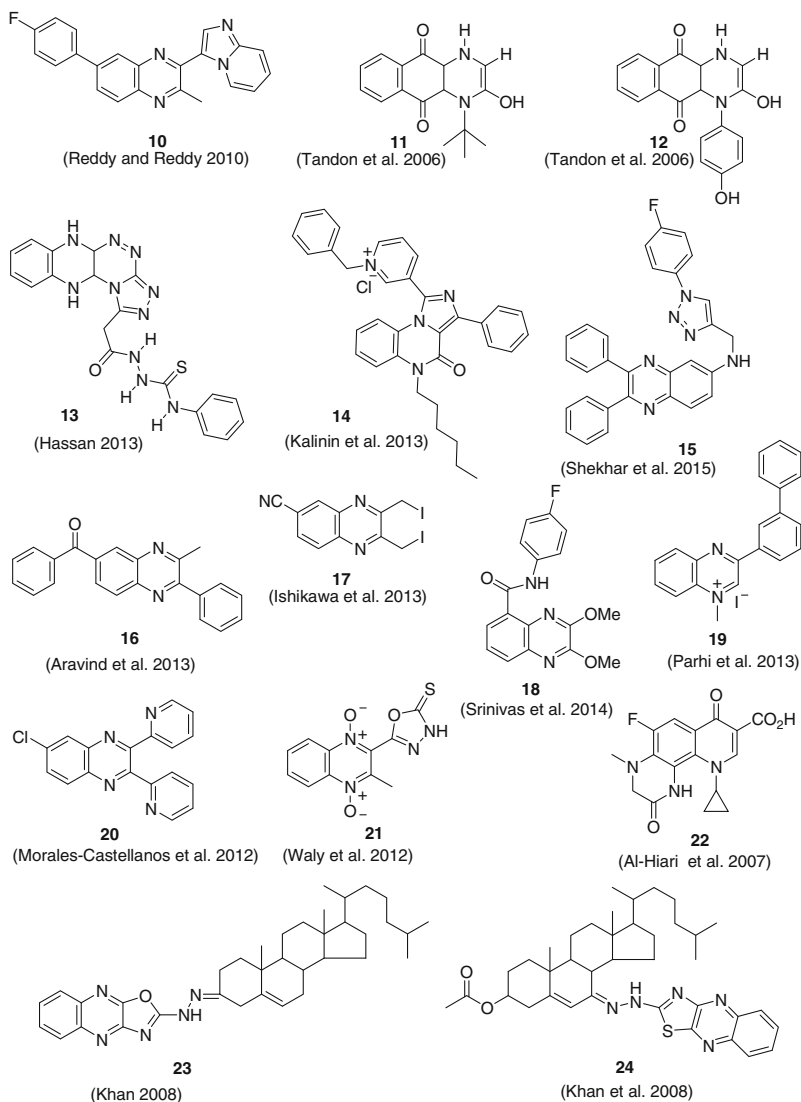


Fig. 2.4 Some quinoxaline motifs with antibacterial activity

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,

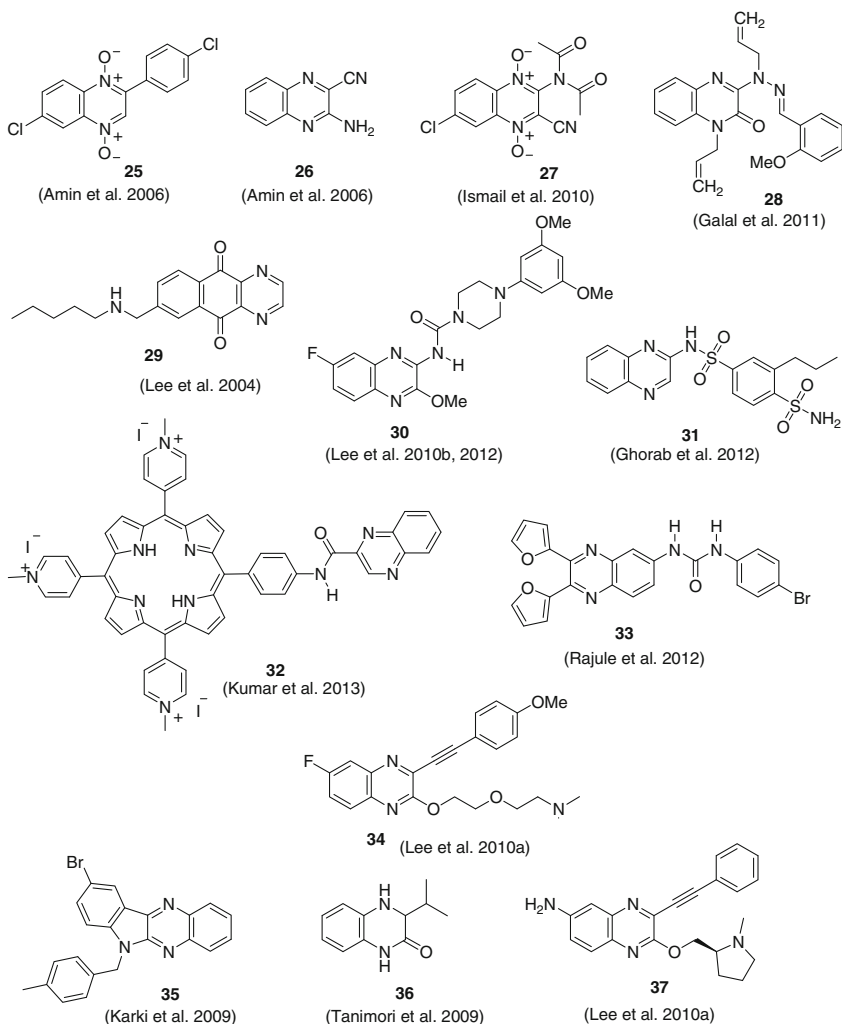


Fig. 2.5 Some quinoxaline motifs with anticancer activity

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.

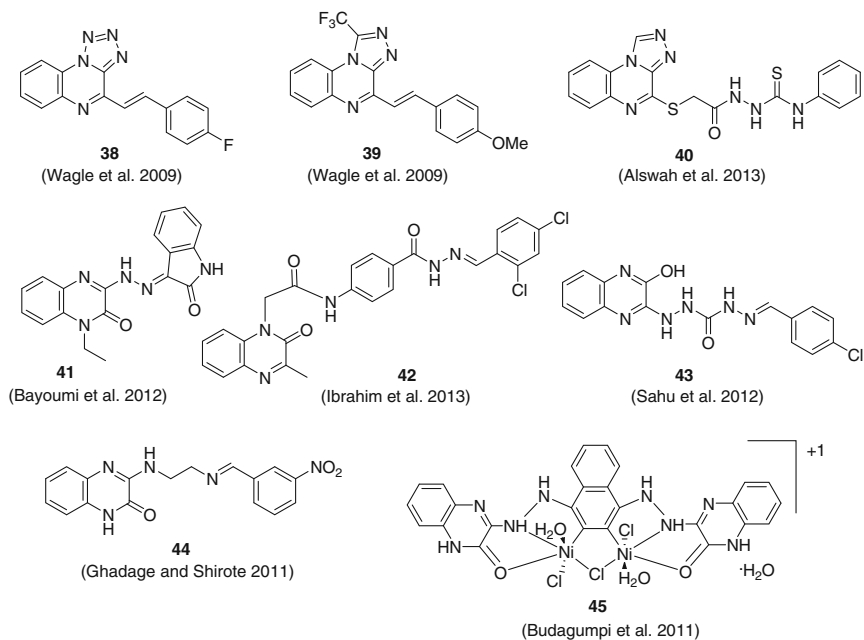


Fig. 2.6 Some quinoxaline motifs with anticonvulsant activity

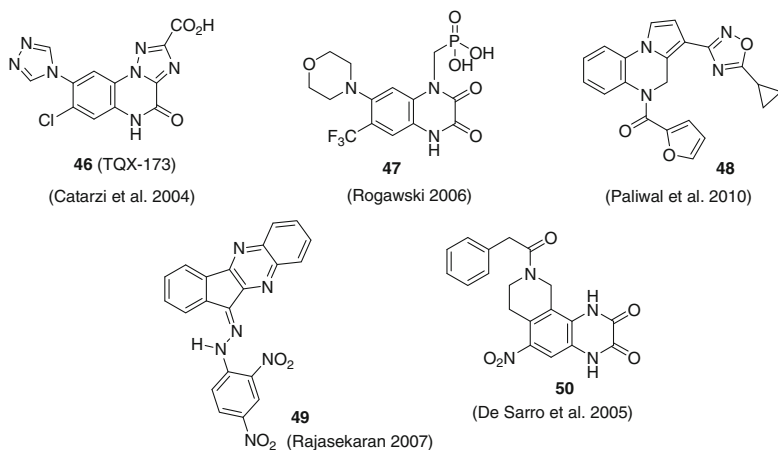


Fig. 2.7 Some quinoxaline motifs with antiepileptic activity

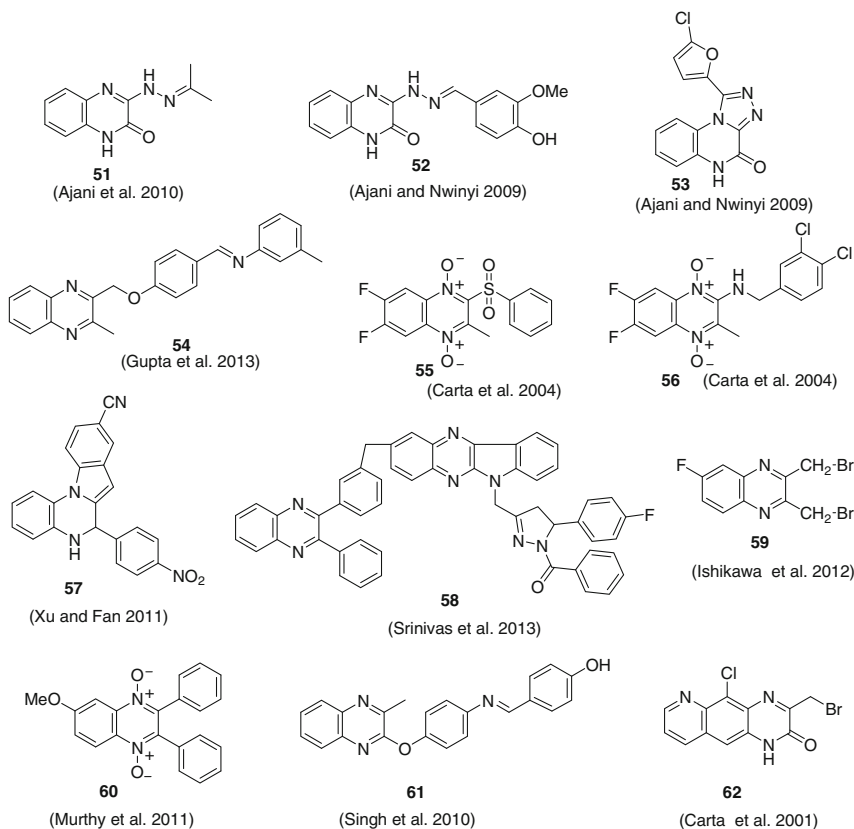


Fig. 2.8 Some quinoxaline motifs with antifungal activity

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

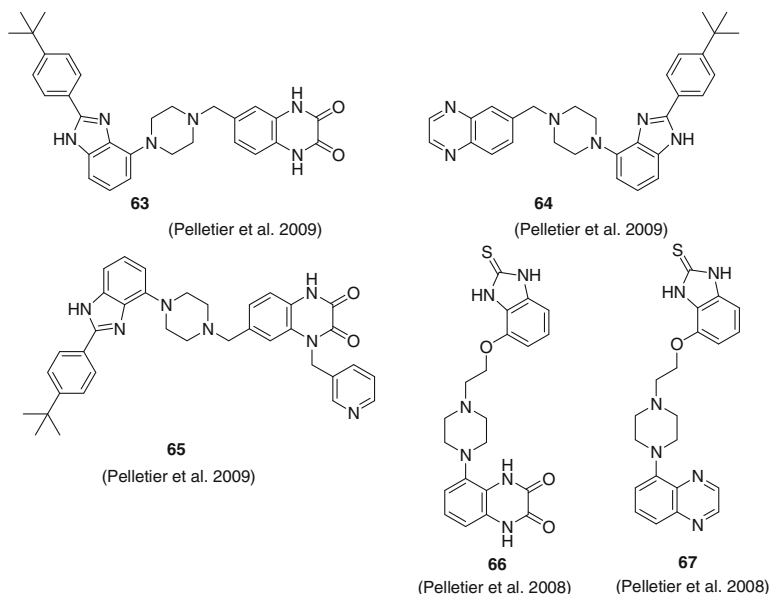


Fig. 2.9 Some quinoxaline motifs with GnRH antagonist activity

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 benzo-quinoxalinone 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 phenylglyoxylate **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).

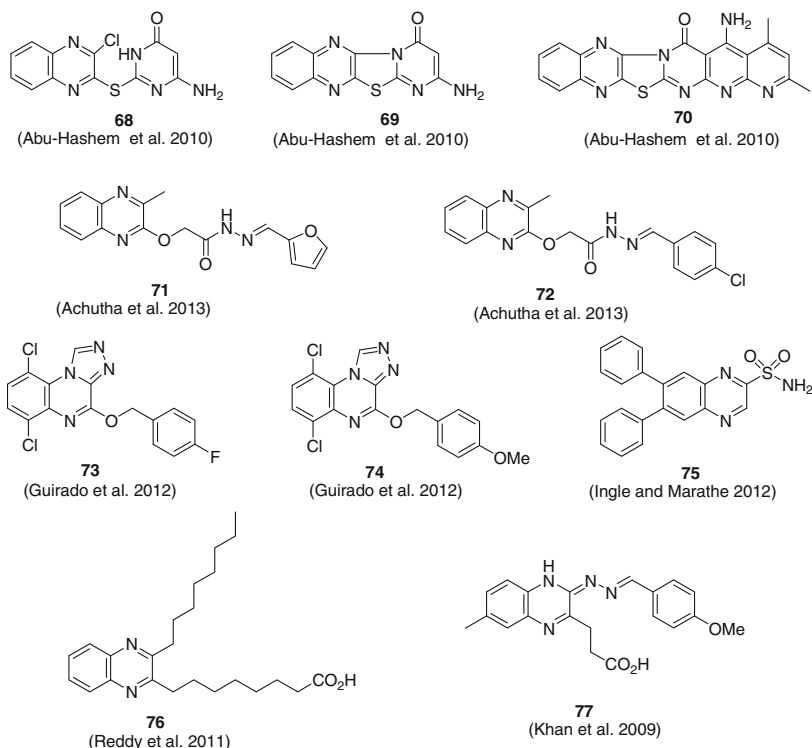


Fig. 2.10 Some quinoxaline motifs with anti-inflammatory and analgesic activities

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

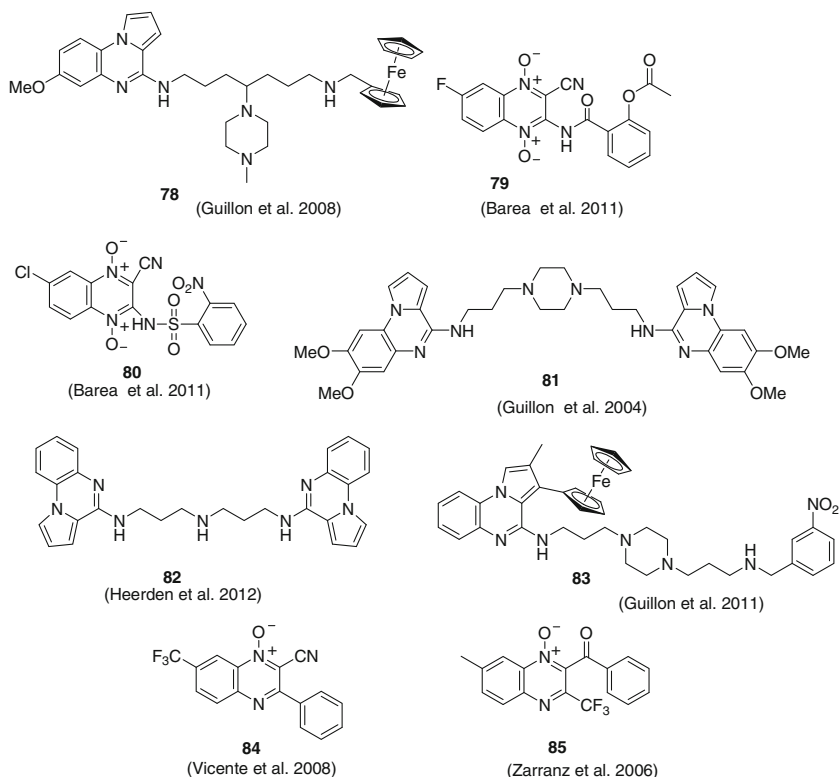


Fig. 2.11 Some quinoxaline motifs with antimalarial activity

(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, PhNH₂, and NaN₃ 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).

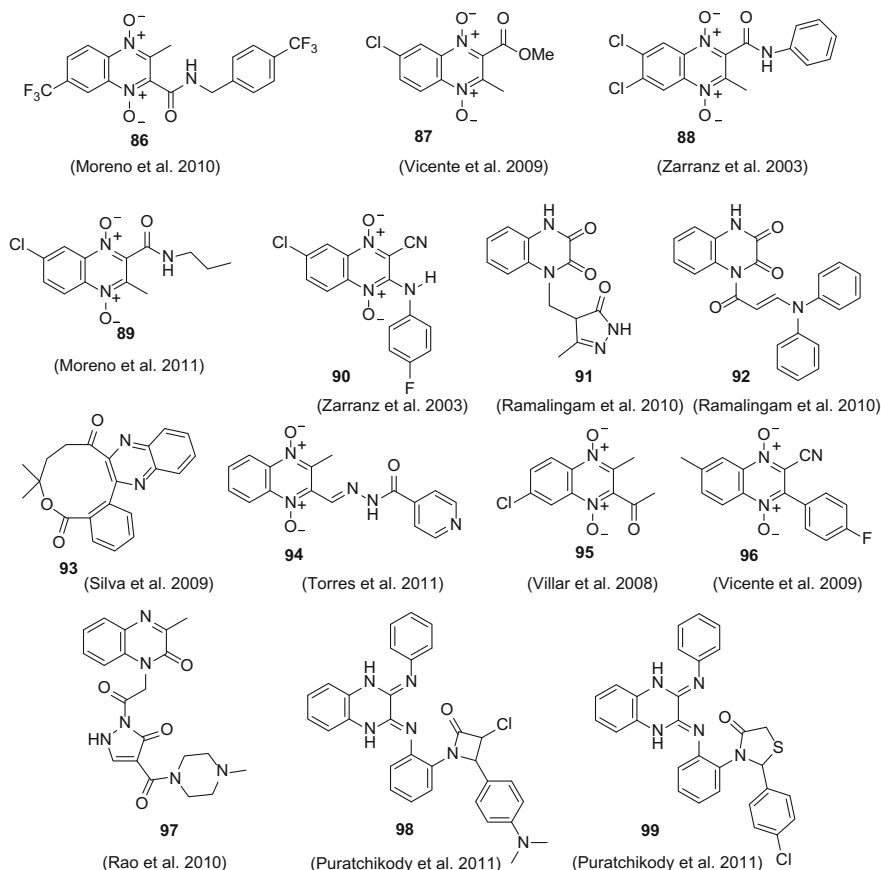
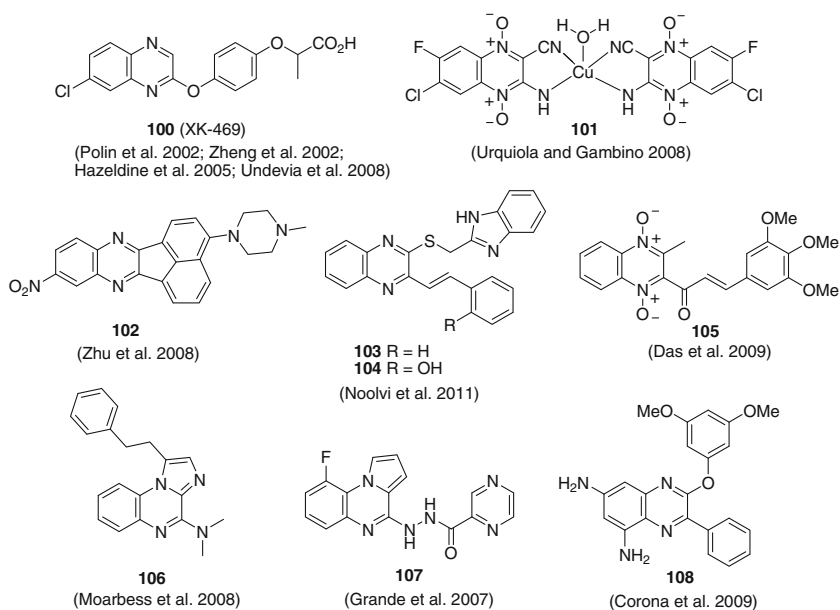
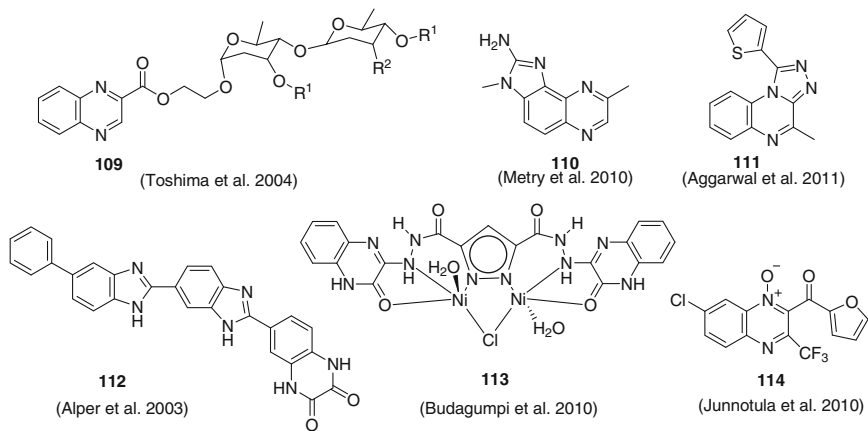


Fig. 2.12 Some quinoxaline motifs with antitubercular activity

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

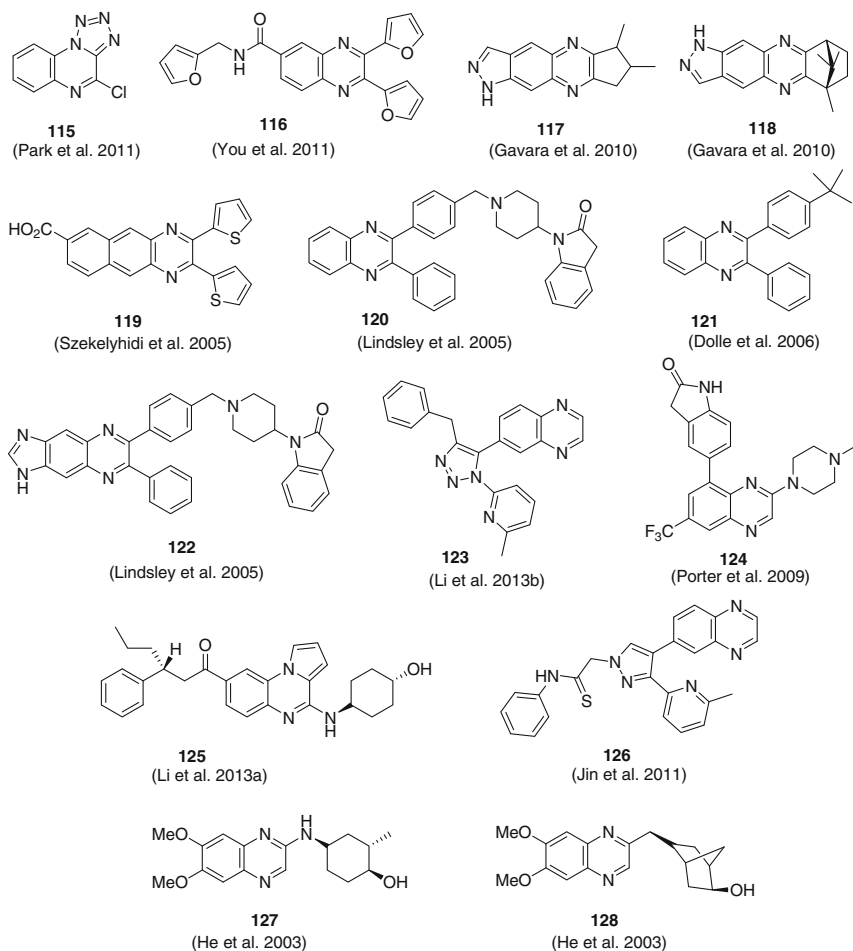


Fig. 2.15 Some quinoxaline motifs with kinase inhibitory activity

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).

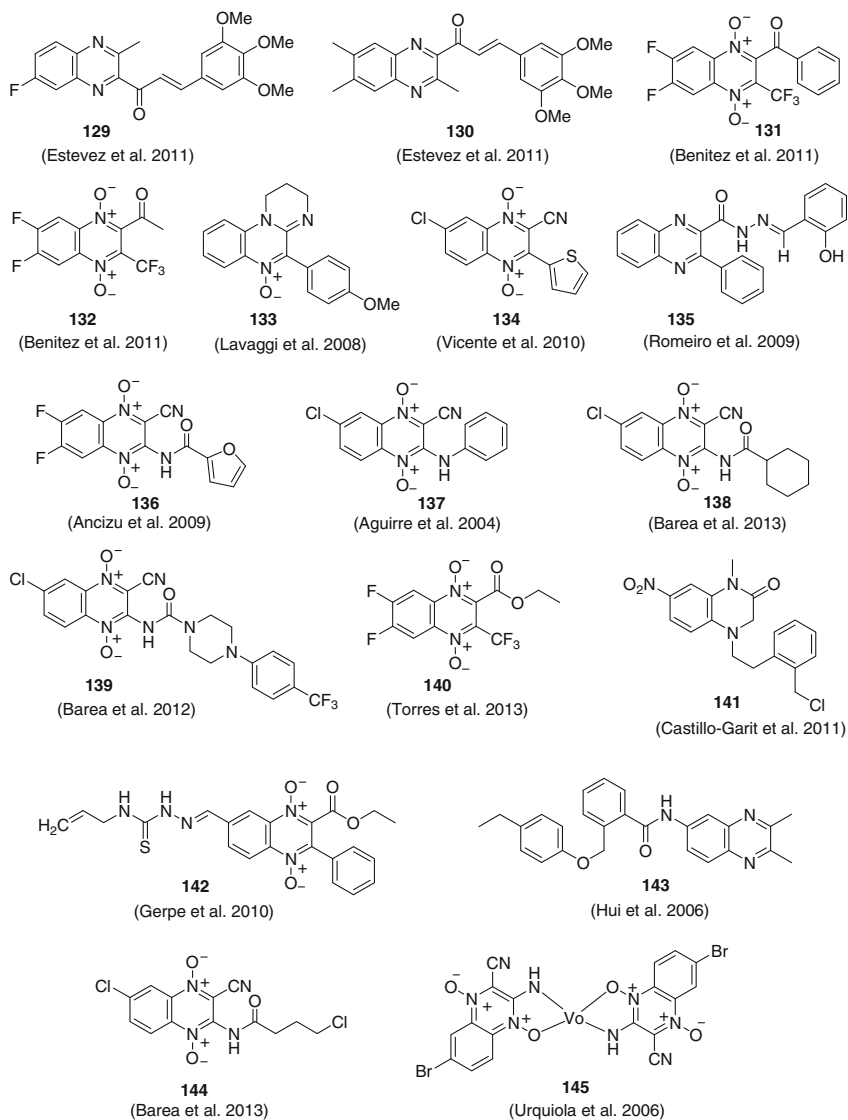


Fig. 2.16 Some quinoxaline motifs with trypanocidal properties

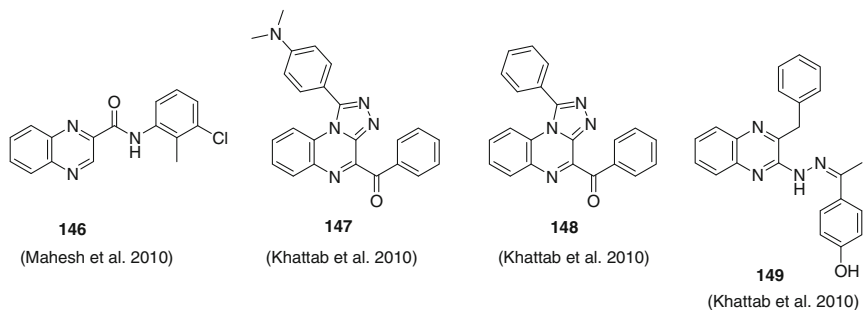


Fig. 2.17 Some quinoxaline motifs with antidepressant activity

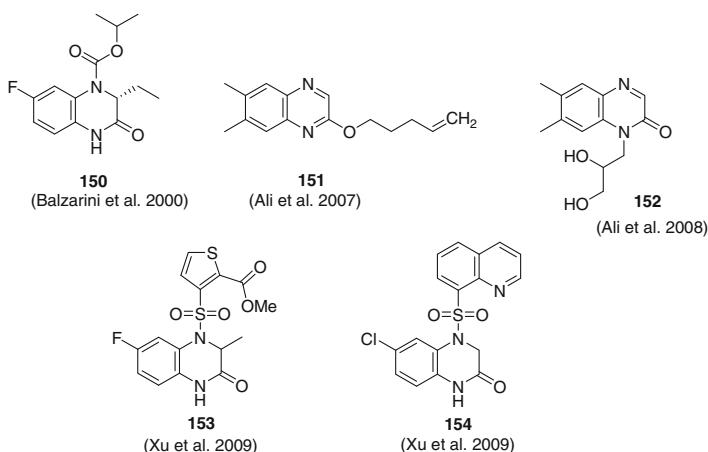
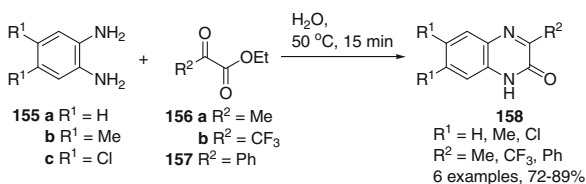


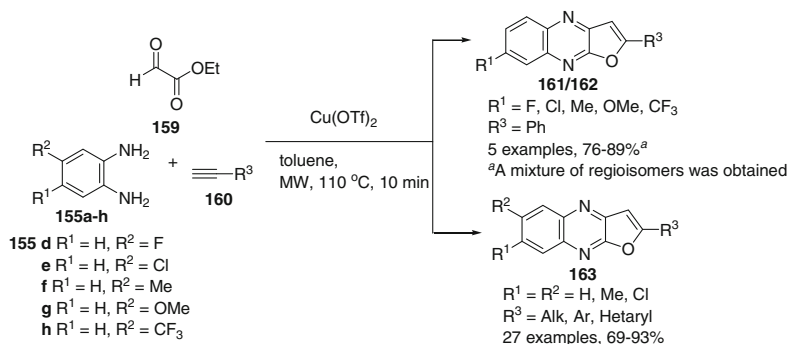
Fig. 2.18 Some quinoxaline motifs with anti-HIV activity

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

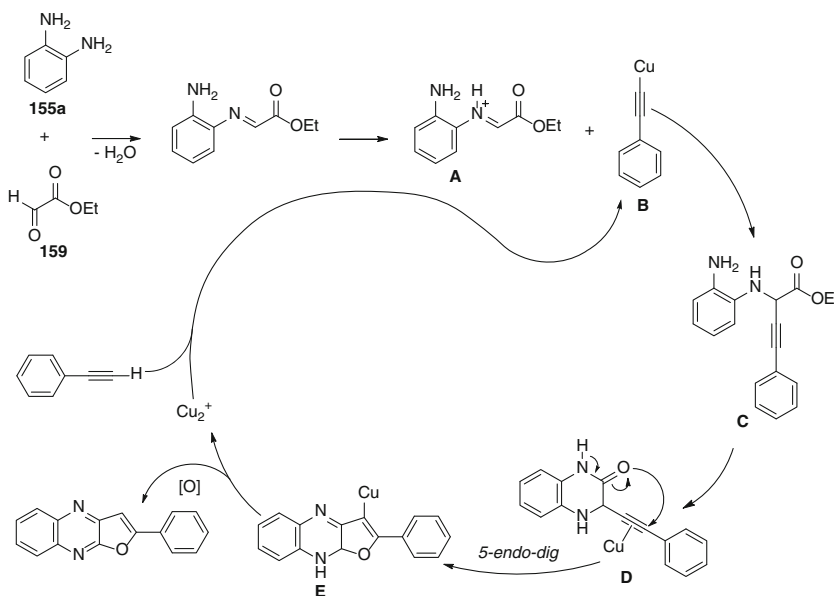


2.2.2 With α -Diketones (1,2-Diketones)

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;

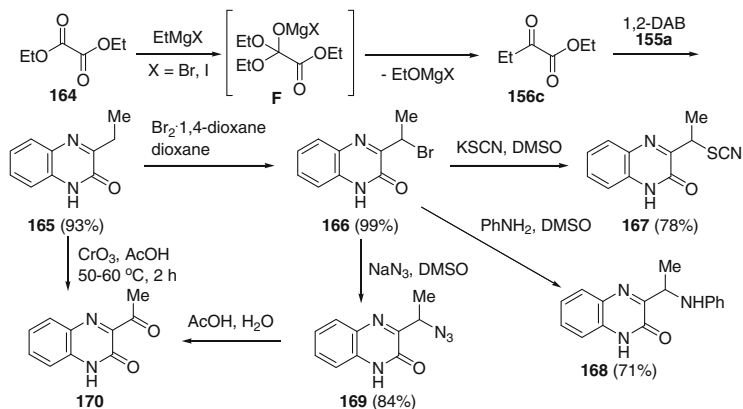


Scheme 2.2 Substrate scope for the synthesis of furoquinoxalines **161–163** with terminal alkynes under optimized conditions

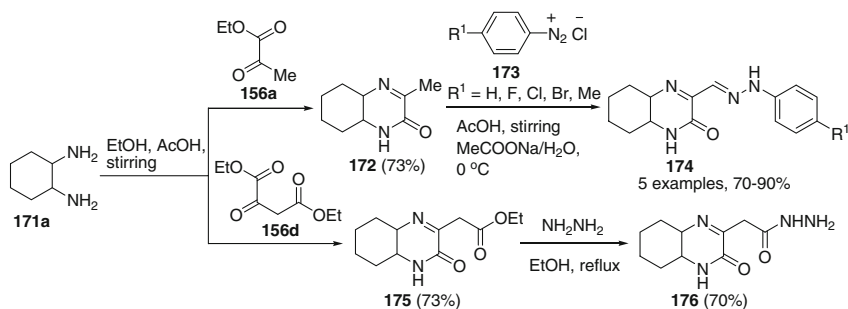


Scheme 2.3 Possible reaction mechanism for the tandem A3-coupling and 5-endo-dig cyclization

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.

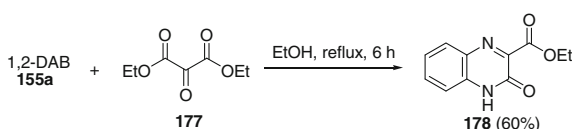


Scheme 2.4 The synthesis and side-chain functionalization of 3-ethylquinoxalin-2(1H)-one **165**



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

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



2009), zirconium(IV) chloride (Aghapoor et al. 2010), niobium(V) chloride (Hou et al. 2010), silica-supported antimony(III) chloride ($\text{SbCl}_3/\text{SiO}_2$) (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 ($\text{H}_6\text{P}_2\text{W}_{18}\text{O}_{62}\cdot 24\text{H}_2\text{O}$) (Heravi et al.

2007), Keggin-type heteropolyacid ($\text{H}_4\text{SiW}_{12}\text{O}_{40}$) (Huang et al. 2009), ionic liquid 1-*n*-butylimidazolium tetrafluoroborate (Potewar et al. 2008), Brønsted acid ionic liquid $[(\text{CH}_2)_4\text{SO}_3\text{HMIM}][\text{HSO}_4]$ (Beheshtiha et al. 2010), nano- TiO_2 (Mirjalili and Akbari 2011), $\text{TiO}_2\text{-P25-SO}_4^{2-}$ (Krishnakumar and Swaminathan 2010), $\text{TiO}_2\text{-SO}_4^{2-}$ (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).

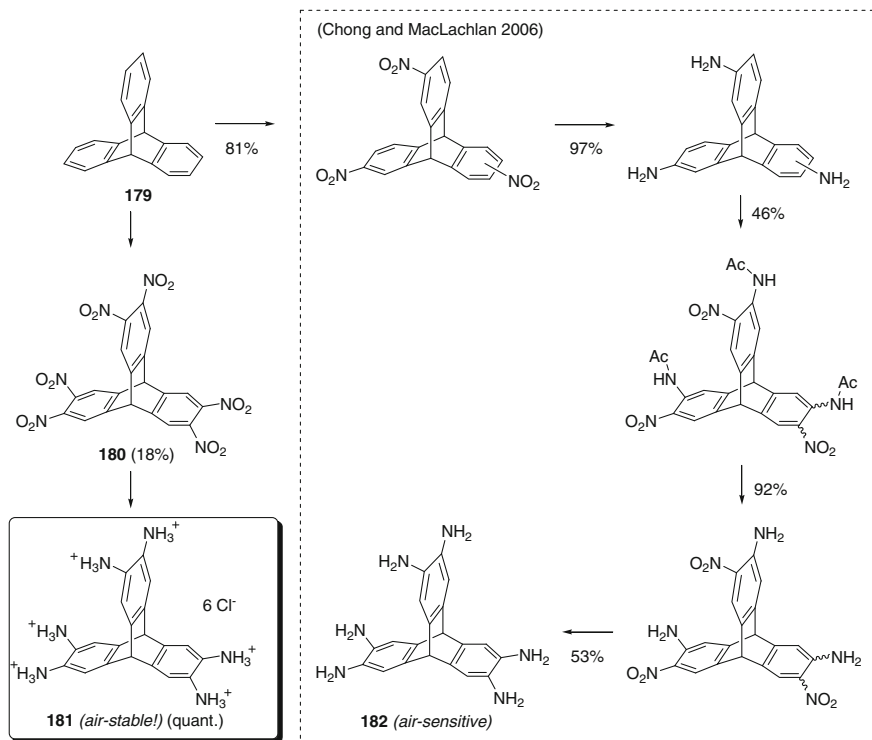
When symmetric α -diketones and symmetric 1,2-DAB derivatives and unsymmetric α -diketones and symmetric 1,2-DAB derivatives, and vice versa, have been used, the symmetric α -diketones and unsymmetric 1,2-DAB derivatives always exclusively produce one regioisomer (Carta et al. 2003; Zhao et al. 2004; 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

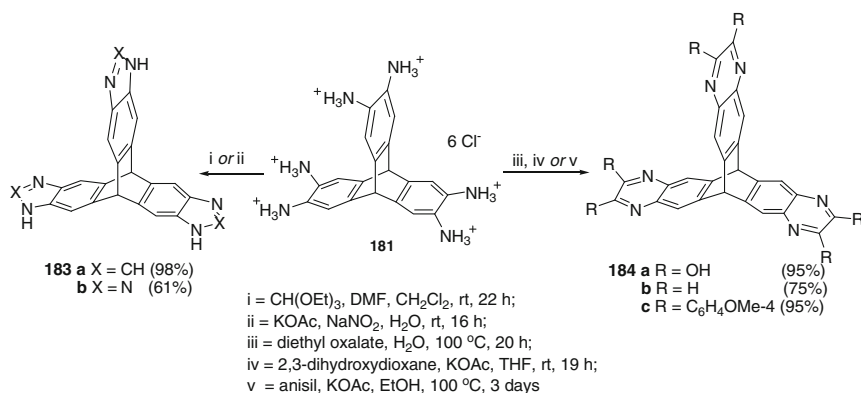
normal α -dicarbonyl compounds, and (c) fused compounds containing α -dicarbonyl and fused compounds containing 1,2-diamino groups can be used. All these combinations lead to condensed quinoxalines derivatives. In these cases the reaction conditions can be different, e.g., heating the reactants in refluxing 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 $\text{TiO}_2\text{-P}25\text{-SO}_4^{2-}$ (Krishnakumar and Swaminathan 2010), $\text{TiO}_2\text{-SO}_4^{2-}$ (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-hexaammoniumtritycene 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 ^1H NMR spectroscopy it can be estimated that the desired hexanitrotritycene **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 ^1H NMR spectroscopy).

The reduction using tin(II) chloride in aqueous hydrochloride/ethanol solution was carried out for the subsequent sixfold transformation of the hexanitrotritycene **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 hexaammoniumtritycene hexachloride **181** as a synthetic analog of hexaminotriptycene **182**

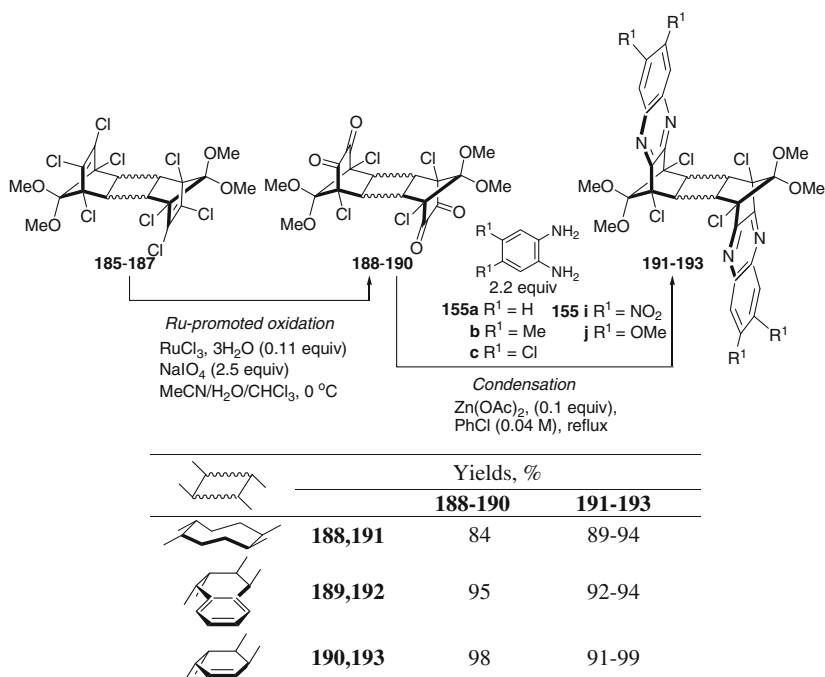


Scheme 2.8 Reactions of hexaammonium salt **181** in condensation reactions

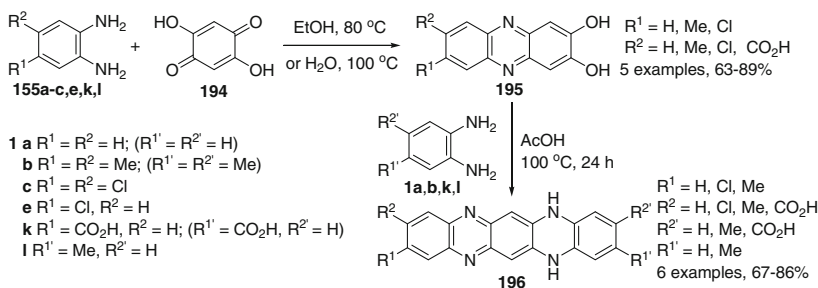
derivative-2,3,6,7,12,13-hexahydroxy-2,6,12-trihydrotritypy[2,3-d:6,7-d':12,13-d''] tripyrazyl **184a** can be prepared by the reaction of the hexaammonium salt **181** with diethyloxalate in water at 100 °C, giving the product as a pale yellow solid in high yield (95 %). For the reaction of **181** with dihydroxydioxane or anisil to the corresponding quinoxalines 2,6,12-trihydrotritypy[2,3-d:6,7-d':12,13-d'']tripyrazyl **184b** and 2,3,6,7,12,13-hexa(4'-methoxyphenyl)-2,6,12-trihydrotritypy-[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



Scheme 2.9 Synthesis of quinoxaline-annulated 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).

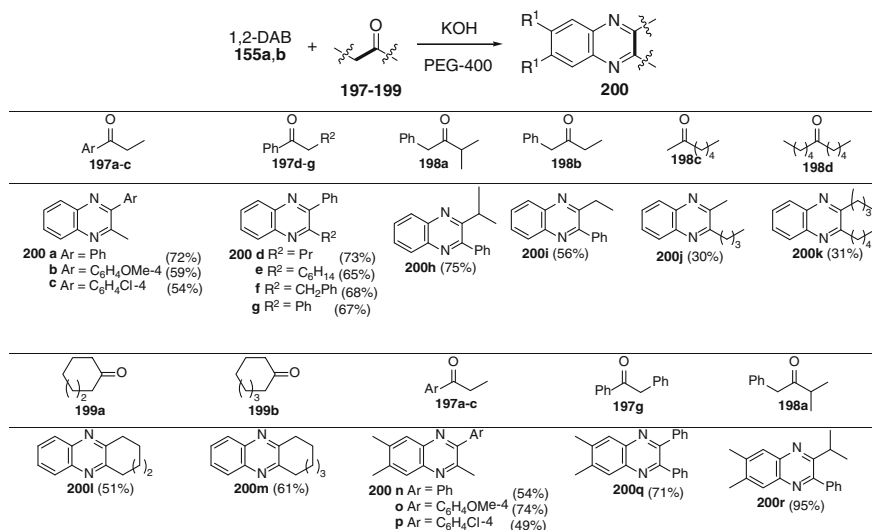
An efficient and practical route to a novel fluorescent benzo[*a*]pyrano[2,3-*c*]phenazine framework has been developed by a one-pot, four-component reaction of 2-hydroxynaphthalene-1,4-dione, 1,2-DABs, aromatic aldehydes, and Meldrum's acid in glacial acetic acid at 70 °C (Saluja et al. 2014).

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

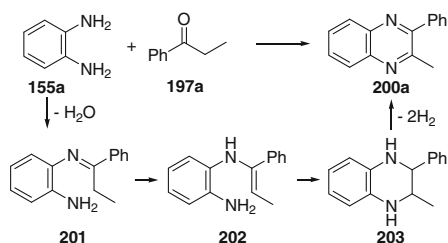
In air, 1,2-DABs **155a, b** react with an array of ketones **197–199** in PEG-400 at 60 °C in the presence of KOH to afford the corresponding quinoxalines **200** in good yields (Scheme 2.11) (Cho et al. 2007).

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



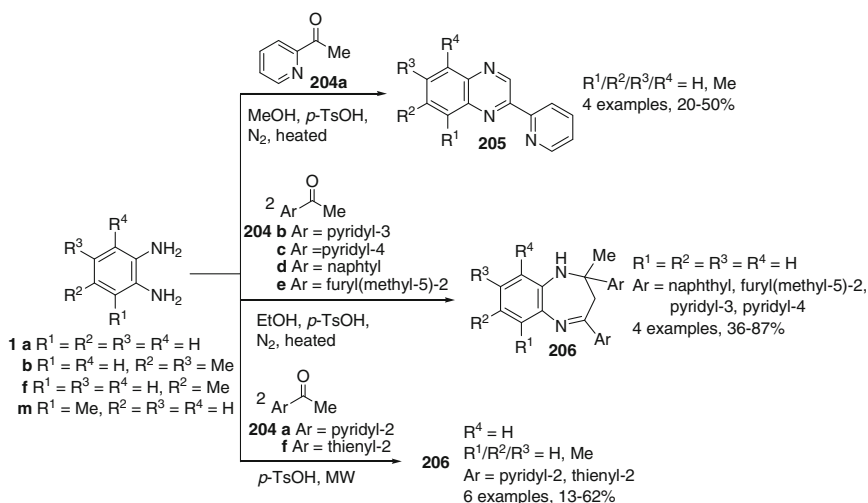
involve intramolecular hydroamination giving a 1,2,3,4-tetrahydroquinoxaline **203**, and then dehydrogenated to give **200a** (Scheme 2.12).

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

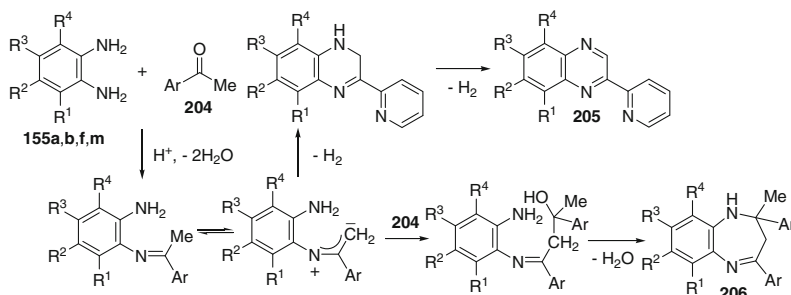
quinoxaline was observed with **198c**. Cyclic ketones such as cycloheptanone **199a** and cyclooctanone **199b** also reacted with **155a** to give 7,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]quinoxaline **200l** and 6,7,8,9,10,11-hexahydrocycloocta[*b*]quinoxaline **200m** in 51 and 61 % yields, respectively. 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).

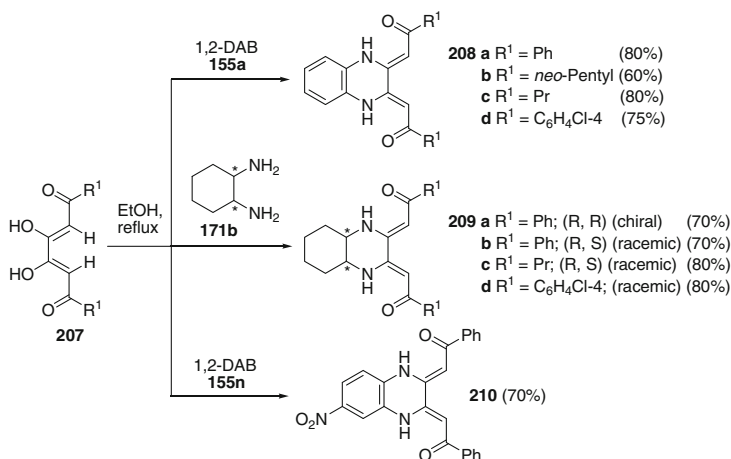
2.2.4 With Hexane-1,3,4,6-tetraones

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 ¹H 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**

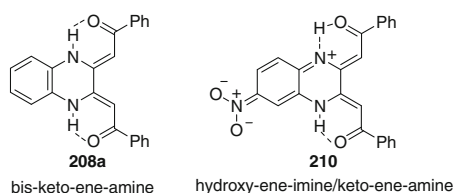
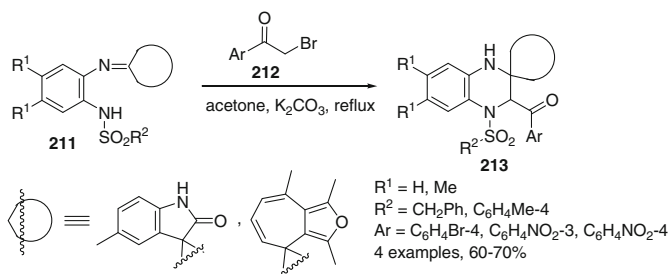


Fig. 2.19 Structures of compound **208a** and **210** as confirmed by X-ray crystallography and deduced from the theoretically limiting forms

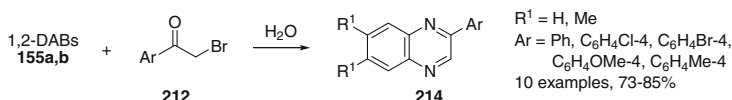
Kumar and Pawar 2004; Gu et al. 2005) formed by reaction with the carbonyl group only, or with dihydroquinoxaline derivatives (Das et al. 2007; Chou et al. 2011). Thus, these reactions are usually carried out in the presence of oxidants or under conditions that promote oxidation (Wu and Ede 2001; Singh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

Alkylation of *o*-(*N*-sulfonylamino)phenylimino 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** ($R = \text{H}$) and phenacyl bromide **212a** ($\text{Ar} = \text{Ph}$) as model substrates to synthesize 2-phenylquinoxaline **214a** ($\text{Ar} = \text{Ph}$) (Scheme 2.17). With the advantages of using a greener solvent in mind, water was employed as the



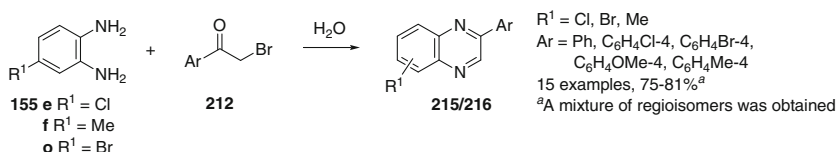
Scheme 2.16 The synthesis of spiro-quinoxalines **213**



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.



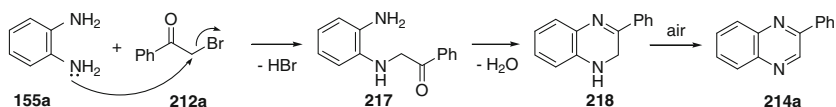
Scheme 2.18 Reactions of unsymmetrical diamines with phenacyl bromides

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.

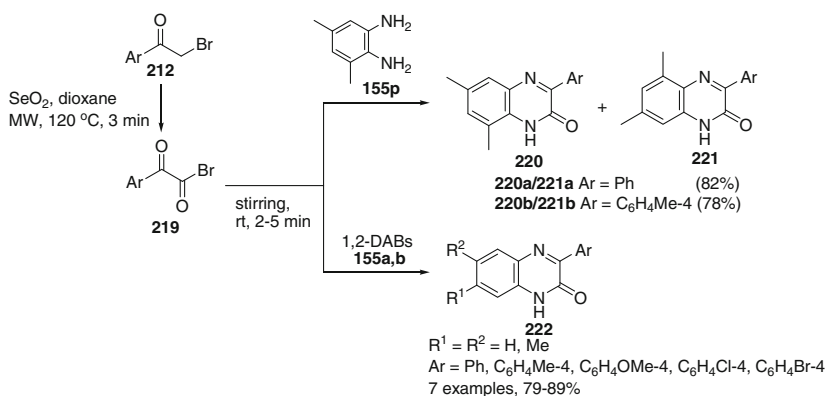
α -Bromoketones **212** undergo selenium dioxide oxidation to yield reactive 2-oxo-2-arylacetyl bromides **219** that are trapped by 1,2-DABs **155a, b, p**, to give quinoxalinones **220–222**, in good yield (Nagaraj et al. 2013) (Scheme 2.20).

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).

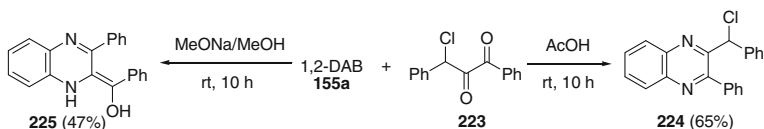
The reactions of 1,2-DAB **155a** with 3-aryl- and 3-alkyl-3-chloropyruvate esters **156e** afford quinoxalin-2-(1*H*)-ones **226** (Scheme 2.22) (Mamedov et al. 1989, 2010; Saifina et al. 2009). In this case, the formation of the quinoxaline ring involves the α -keto group of the ester rather than the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



Scheme 2.19 Plausible reaction mechanism

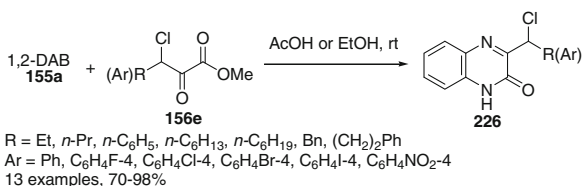


Scheme 2.20 Synthesis of quinoxalinones from 2-oxo-2-aryl acetyl bromides **219**



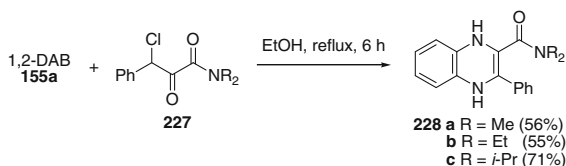
Scheme 2.21 The reaction of 3-chloro-1,3-diphenylpropane-1,2-dione **223** with 1,2-DAB **155a** under various conditions

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

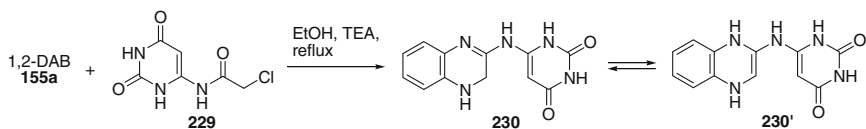


In the case of 3-chloro-3-phenylpyruvamides **227**, reaction with 1,2-DAB **155a** involves the α -chloro ketone fragment, giving rise to 1,4-dihydroquinoxalines **228**. These are due to the relatively easy alkylation of the amino group, unlike the transamidation of the amide group (Scheme 2.23) (Mamedov 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 quinoxaliny-C(3)-CH₂- and quinoxaliny-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).

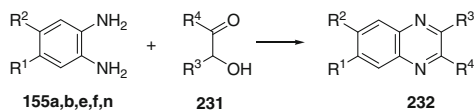
2.2.7 With Vicinal Diols

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

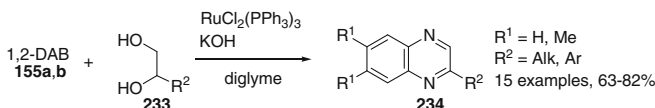
A fast and efficient method which is associated with the use of dialkyl acetylenedicarboxylates and 1,2-DAB, mild conditions, producing excellent yields, was established for the synthesis of quinoxalin-2(1*H*)-ones in water under catalyst-free conditions. The reactions of 1,2-DAB **155a** and naphthalene-2,3-diamine (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).

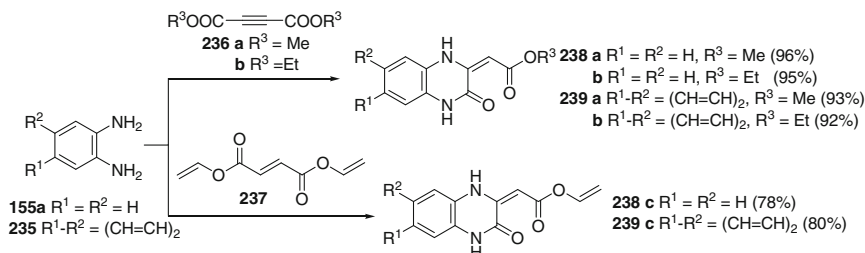
Table 2.1 One-pot synthesis substituted quinoxalines from hydroxy ketones

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	<i>c</i> -Hexyl	85	78	–	–
6	232f	Me	Me	H	Ph	75	66	–	29 ^a 89 ^b
7	232g	Me	Me	H	<i>c</i> -Hexyl	80	89	–	–
8	232h	Me	Me	H	(CH ₂) ₄ Me	60	62	–	–
9	232i	H	H	H	C ₆ H ₃ -di-Cl-2,4	75	–	–	–
10	232j	H	H	H	C ₆ H ₄ Cl-4	80	–	–	–
11	232k	H	H	H	C ₆ H ₄ F-4	82	–	–	–
12	232l	Me	Me	H	C ₆ H ₃ -di-Cl-2,4	83	–	–	–
16	232m	H	H	H	C ₆ H 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 ₆ H ₄ Me-4	C ₆ H ₄ Me-4	–	–	95	–
20	232q	H	H	C ₆ H ₃ -di-Cl-2,4	C ₆ H ₃ -di-Cl-2,4	–	–	94	–
21	232r	H	H	C ₆ H ₄ OMe-4	C ₆ H ₄ OMe-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	–

^aMicrowave conditions open vessel^bMicrowave conditions closed vessel

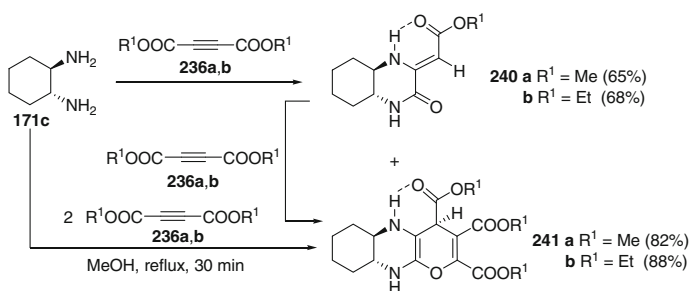


Scheme 2.25 A ruthenium-catalyzed approach for quinoxalines **234** from 1,2-DABs **155a, b** and vicinal diols **233**



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)-3,4,4*R*,5,6,7,8,8*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*,5*aR*,9*aR*-4*H*-pyrano[2,3-*b*]-5,5*a*,6,7,8,9,9*a*,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

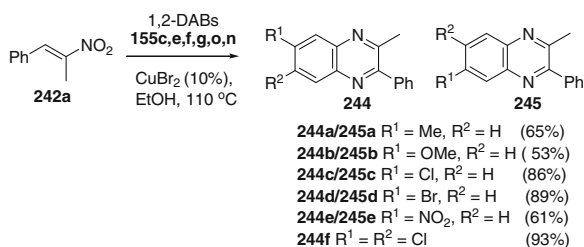
An easy and efficient copper-catalyzed reaction for the synthesis of quinoxalines from 1,2-DABs and nitroolefins has been developed (Chen et al. 2013). This reaction could proceed well enough without any additional base and be applied to various available substrates with a one-step synthetic procedure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

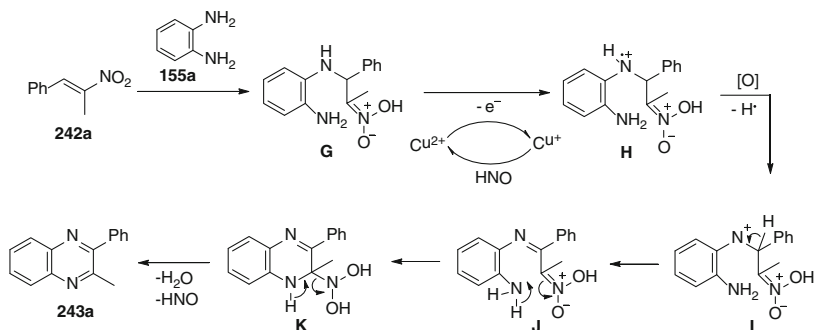
Entry	242	R ¹	R ²	243	Yield (%)
1	242a	Ph	Me	243a	90
2	242b	C ₆ H ₄ Me-4	Me	243b	77
3	242c	C ₆ H ₄ OMe-4	Me	243c	80
4	242d	C ₆ H ₄ OH-4	Me	243d	86
5	242e	C ₆ H ₄ Cl-4	Me	243e	77
6	242f	C ₆ H ₄ Br-4	Me	243f	81
7	242g	C ₆ H ₄ NO ₂ -4	Me	243g	62
8	242h	C ₆ H ₄ CN-4	Me	243h	64
9	242i	C ₆ H ₄ CF ₃ -4	Me	243i	71
10	242j	C ₆ H ₄ OMe-2	Me	243j	35
11	242k	C ₆ H ₄ Cl-2	Me	243k	42
12	242l	C ₆ H ₄ Br-2	Me	243l	42
13	242m	C ₆ H ₄ NO ₂ -4	Me	243m	38
14	242n	C ₆ H ₄ Cl-3	Me	243n	63
15	242o	C ₆ H 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**



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).



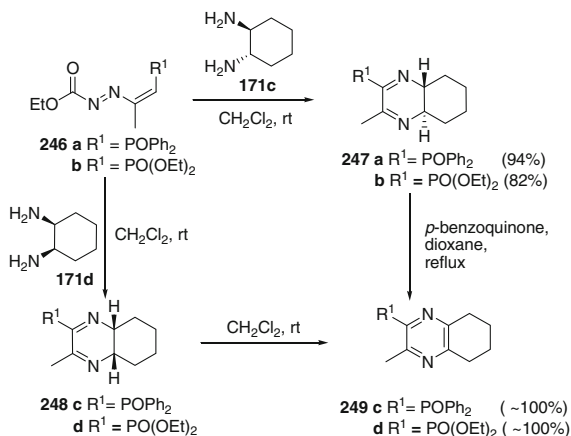
Scheme 2.29 Proposed mechanism

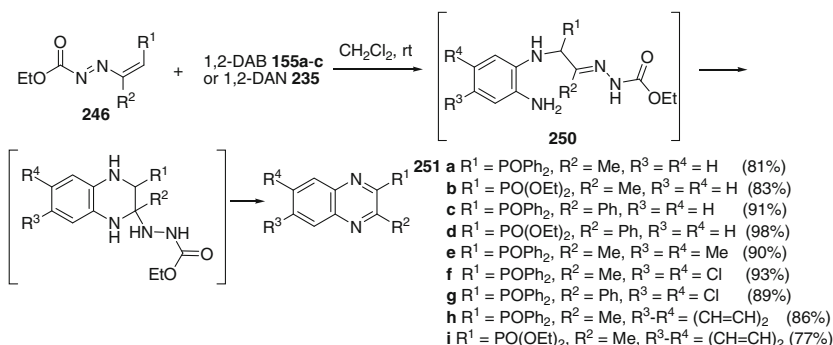
2.2.10 With 1,2-Diaza-1,3-butadienes

The Michael addition of ($\pm$)-*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 ($\pm$)-*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 ($\pm$)-*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 ^1H 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 ($\pm$)-*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.

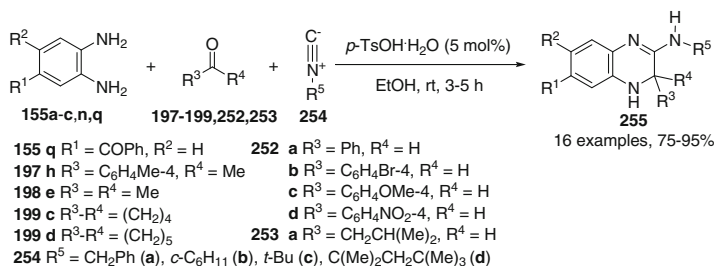
2.2.11 With Ketones(Aldehydes) and Isocyanide

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·H₂O 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 H₂N–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-amine **255** from the MCRs of various diamines **155**, ketones **197–199** or aldehydes **252**, **253**, and isocyanides **254**

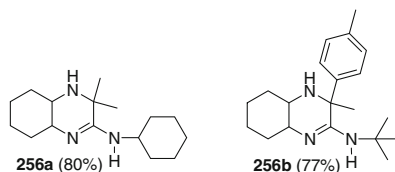


Fig. 2.20 Octahydroquinoxalines **256a**, **b**, produced from the MCRs of 1,2-DACH **171a**, ketones **197h**, **198e**, and isocyanides **254b**, **c**

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-3,4,4a,5,6,7,8,8a-octahydro-3,3-dimethylquinoxalin-2-amine **256a** and *N*-*tert*-butyl-3,4,4a,5,6,7,8,8a-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 ($\text{R}^1\text{--R}^5$) 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 .

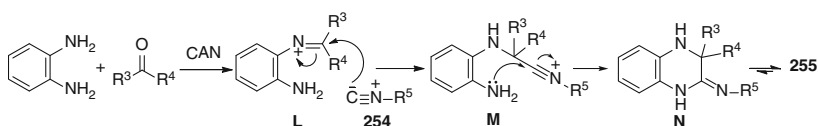
The mechanism has not been unequivocally established, but a possible one is outlined in Scheme 2.26. First, the carbonyl group could be activated by the

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).

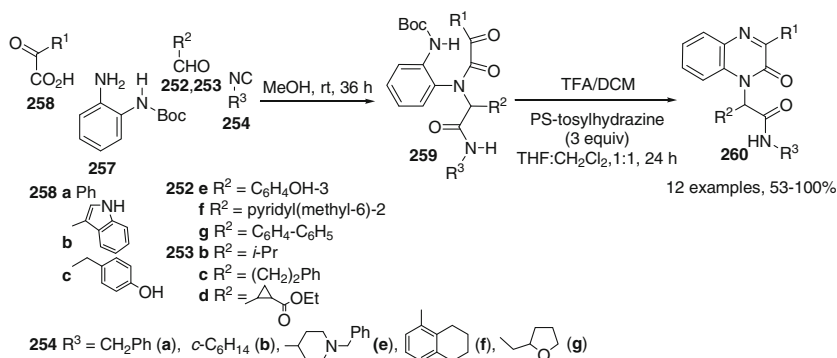
Although Ce(IV) derivatives are generally employed as single-electron transfer (SET) oxidants, the authors (Li et al. 2009a) believe that CAN serves as a Lewis acid in the above process in the same way as in other carbon–carbon and carbon–heteroatom bond-forming reactions (Nair et al. 2004a).

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**

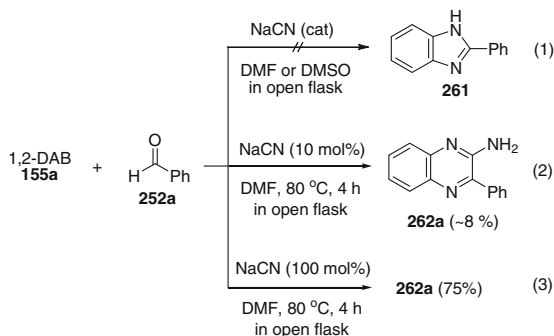


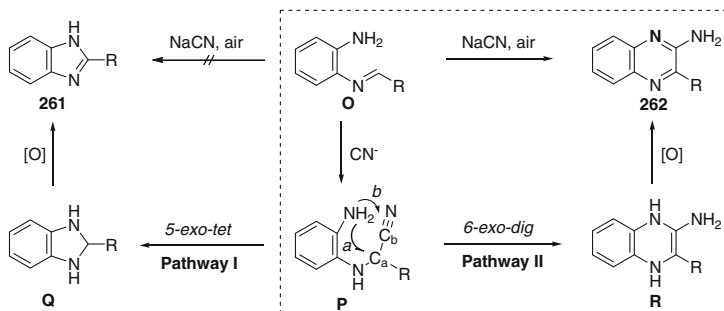
Table 2.3 Substrate scope

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 ₆ H ₄ OMe-4	262b	80
3	155a	H	H	252c	C ₆ H ₄ Me-4	262c	77
4	155a	H	H	252d	C ₆ H ₄ Cl-4	262d	93
5	155a	H	H	252e	C ₆ H ₄ CO ₂ Me-4	262e	92
6	155a	H	H	252f	C ₆ H ₄ OMe-2	262f	92
7	155a	H	H	252g	C ₆ H ₄ Cl-2	262g	82
8	155a	H	H	252h	C ₆ H ₄ OH-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	<i>n</i> -Hexyl	262n	65
15	155a	H	H	252o	<i>c</i> -Hexyl	262o	60
16	155a	H	H	252p	<i>t</i> -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

^aTwo regioisomers were obtained as an inseparable mixture in a 2:1 ratio^bTwo 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 sp³-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

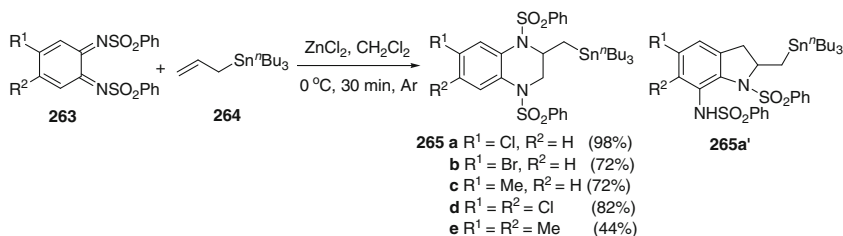
The desired 2-aminoquinoxaline **262** could be obtained after the aerobic oxidation of **R** (Pathway II). Under these conditions, 6-*exo-dig* cyclization would predominantly take place over 5-*exo-tet* cyclization presumably due to a better orbital orientation between HOMO and LUMO, which led to the 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

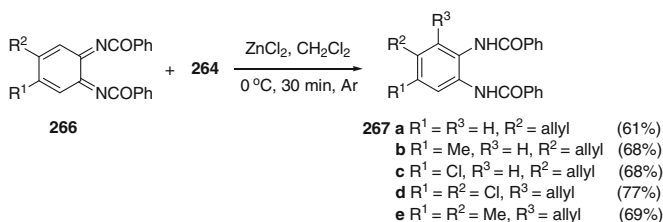
2.3.1 With Allylstannane

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*-quinonediiimines, 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** ($R^1 = \text{Cl}$, $R^2 = \text{H}$) 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).



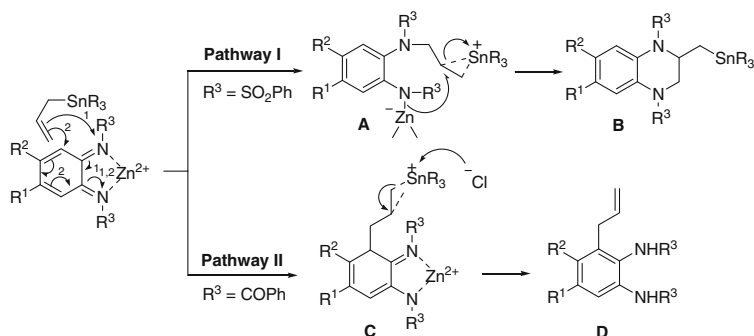
Scheme 2.37 Lewis acid-promoted annulation of *o*-quinonedibenzesulfonimides **263** using allylstannane **264**



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** ($R^1 = R^2 = \text{H}$) 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 tetrahydro-quinoxaline 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

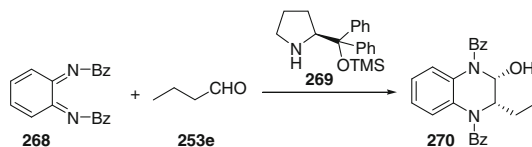
2.3.2 With Aldehydes

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).

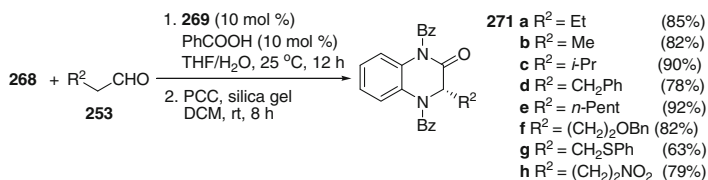
Since the required *o*-benzoquinone diimide was easily accessible by benzylation of commercially available 1,2-DAB derivative and subsequent oxidation, it appears possible that a search for more appropriate methods of carrying out HDAR to synthesize chiral quinoxaline derivatives would be fruitful.

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 HDAR 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**

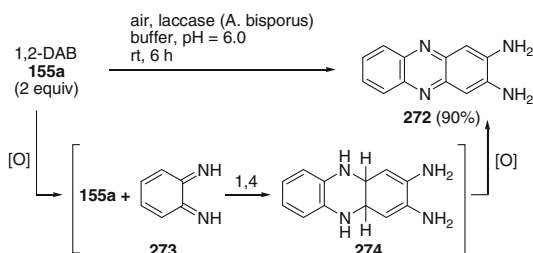
relatively stable compound with excellent stereoselectivity (ee 97 %) and good yield (71 %). Even more satisfactory yields could be attained in a mixture of 1,4-dioxane/ H_2O (ee > 99 %, yield 83 %) or THF/ H_2O (ee > 99 %, yield 89 %) (10:1).

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**



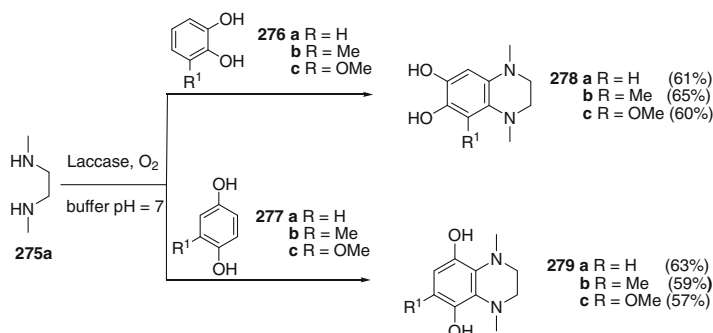
analytical scale this reaction has been employed for determining the activity of laccases (Zuyun et al. 1998). Alternatively, this transformation can also be performed on a preparative scale with either FeCl_3 (Chauhan et al. 2008) or hydrogen peroxide in the presence of catalytic amounts of peroxidases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

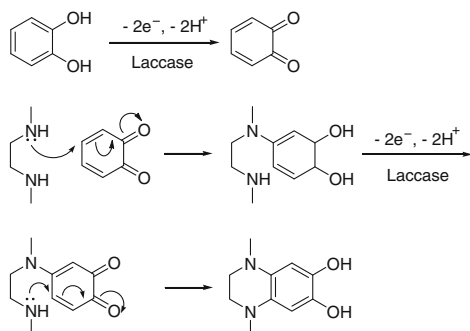
For the mechanistic aspects of this new transformation, the first oxidation of the dihydroxy benzene to the corresponding ketone was assumed to occur followed by an electron-deficient site reaction with diamine. Although intermediate is a 1,2-diketone but in this case, it does not react in a same manner 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.



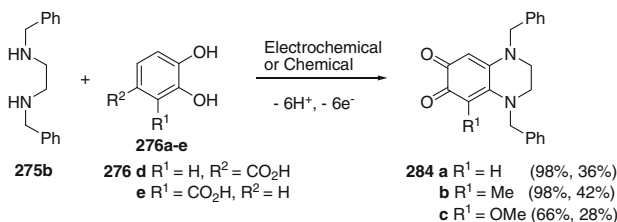
Scheme 2.43 Reaction between *N,N*-dimethylethylenediamine **275a** and different 1,2- and 1,4-dihydroxy benzene **276**, **277** in the presence of laccase at room temperature

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

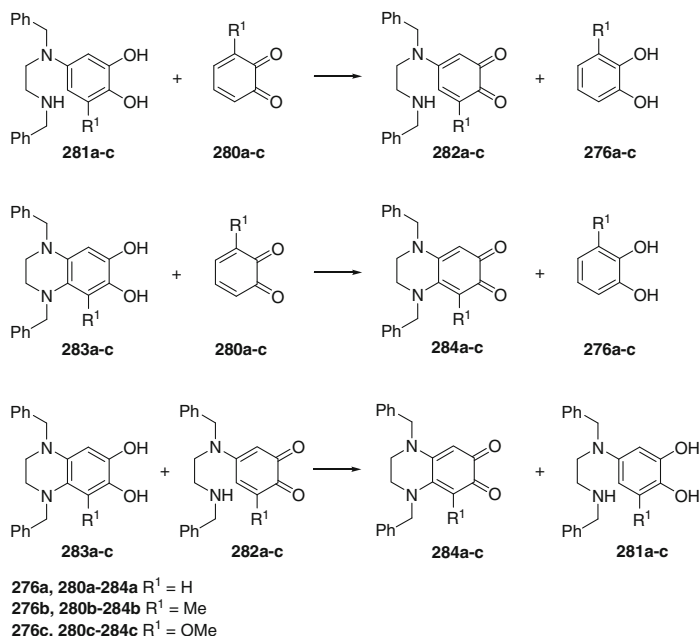


Chemical and electrochemical oxidations of different catechols were carried out in the presence of *N,N'*-dibenzylethylenediamine (DBEDA) in a phosphate buffer/acetonitrile solution for the synthesis of different new dibenzyltetrahydroquinoxalinedione derivatives (Habibi et al. 2014). The oxidation of 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).



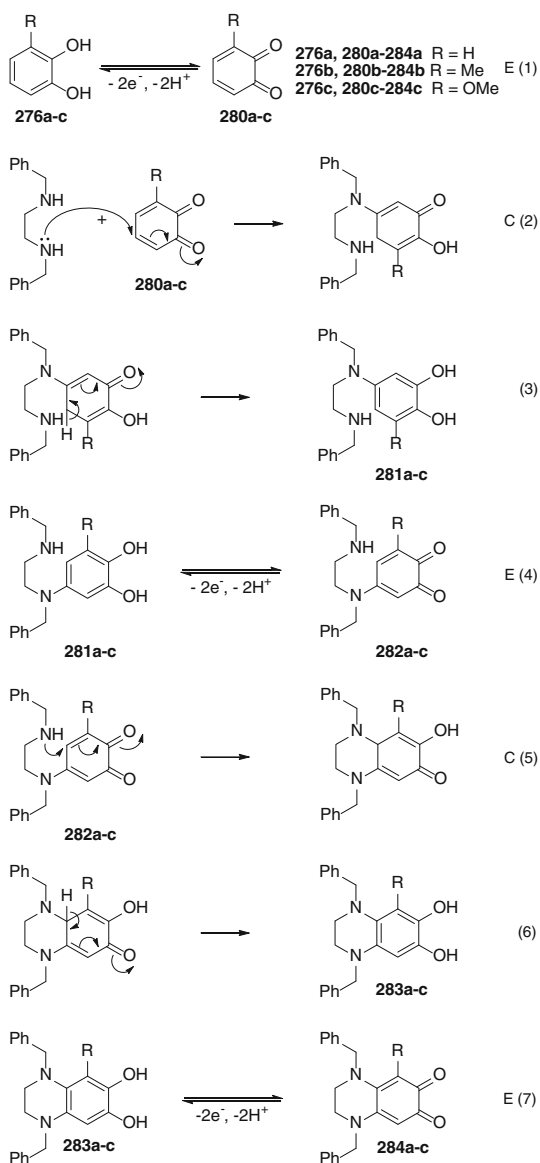
Scheme 2.45 Synthesis of different dibenzyltetrahydroquinoxalinedione derivatives



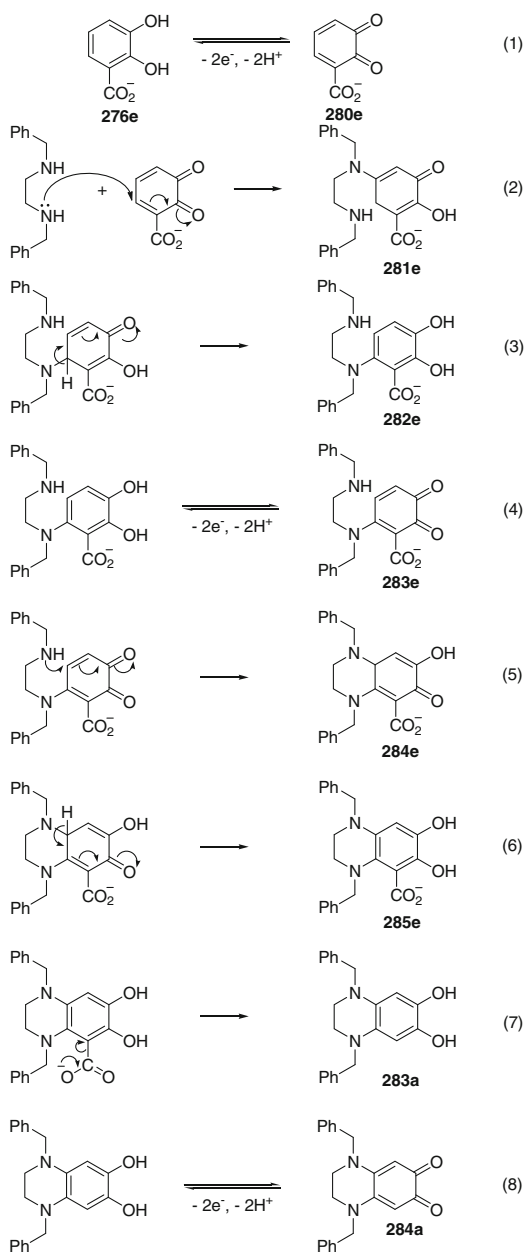
Scheme 2.46 Solution electron transfer reaction

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

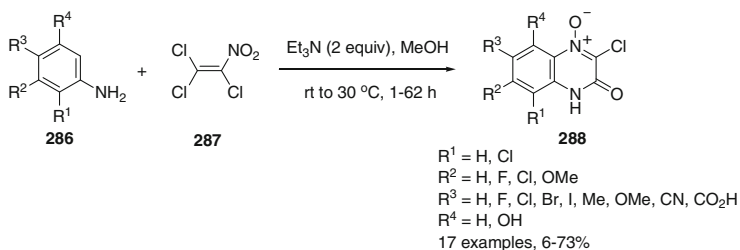


2.5 Synthesis of Quinoxalines from Aniline and Its Derivatives

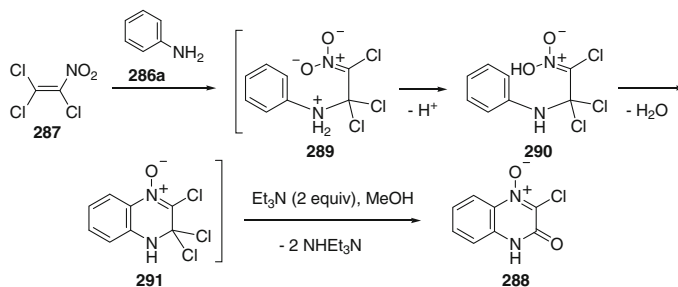
2.5.1 From Anilines

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**

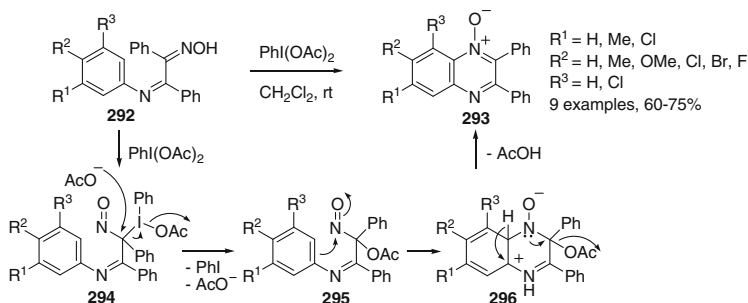


Scheme 2.50 Postulated mechanism for the formation of **288**

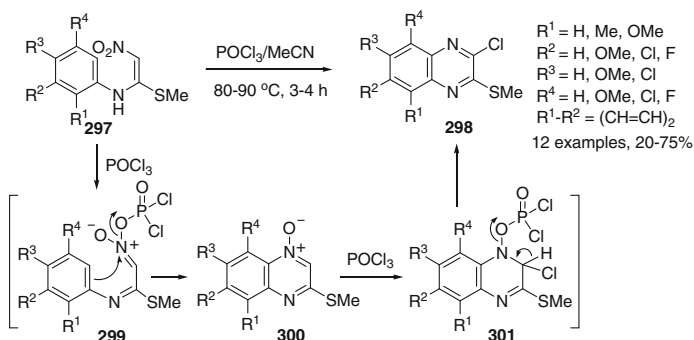
2.5.2 From Benzil- α -arylimino Oximes and α -Nitroketene *N,S*-Anilinoacetals

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 POCl₃, 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**

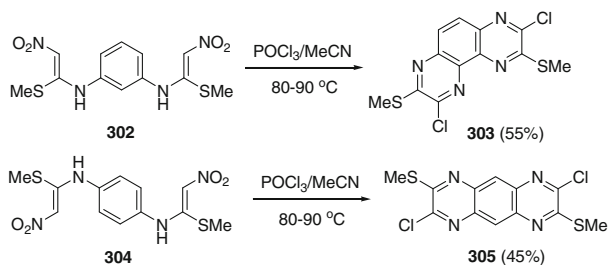


Scheme 2.52 Heteroannulation of nitroketene *N,S*-arylaminoacetals **297** with POCl_3

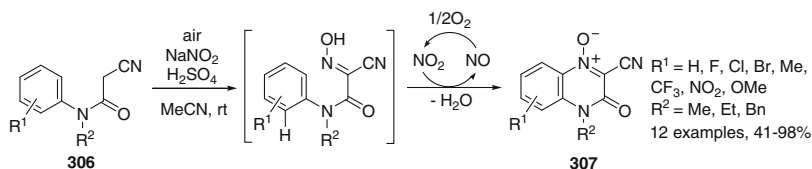
The probable mechanism for the conversion of *N,S*-acetals **297** into quinoxalines **298** involves the initial formation of quinoxaline *N*-oxide **300** by dehydrative cyclization of **297** followed by a subsequent chlorination at the 3-position and the extrusion of oxygen through intermediate **301**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

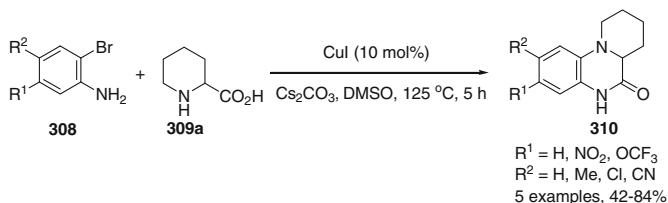
2.5.3 From 2-Haloanilines

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 pipecolic 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).

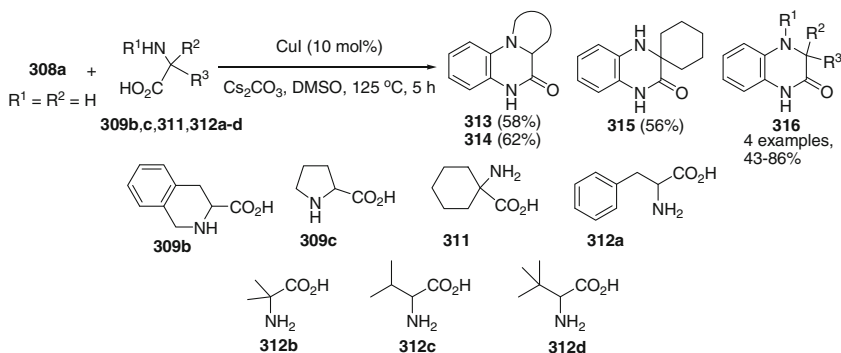
The use of various α -amino acids such as **309b**, **c**, **311**, **312a–d** instead of pipecolic acid **309a** in the reaction with 2-bromoaniline **308a** in the presence of copper(I) iodide made it possible to synthesize various annulated (in the cases of **309b**, **c**), spiro (in the cases of **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).

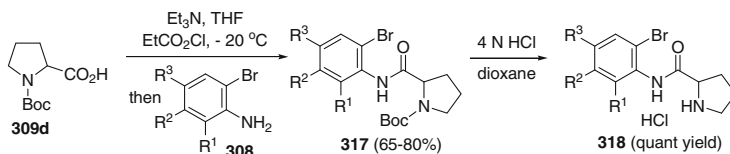
In 2010, Luo and coworkers reported a practical and highly efficient route to the synthesis of pharmaceutically interesting quinoxalinones (Luo et al. 2010). The key step involves an intramolecular palladium-catalyzed *N*-arylation reaction (Buchwald–Hartwig amination Janey 2007; Appukkuttan and Van 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 pipecolic acid **309a**



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

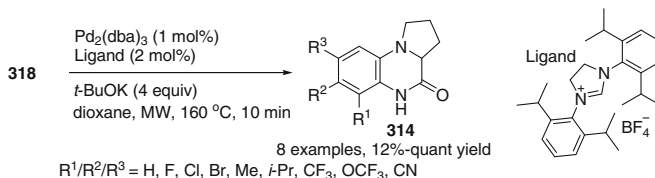


Scheme 2.57 Synthesis of substituted bromoanilides **318**

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 $\text{Pd}_2(\text{dba})_3$, 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.

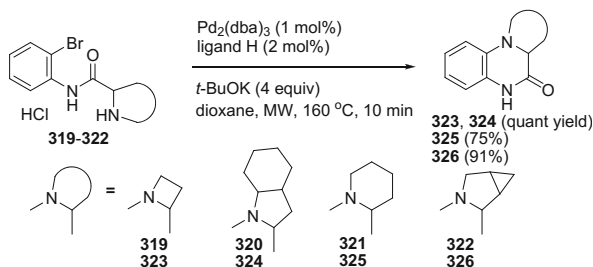
This methodology tolerates a variety of bromoanilides **319–322** to afford a diverse collection of bicyclic and polycyclic quinoxalinones **323–326** in high yields (Scheme 2.59).

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



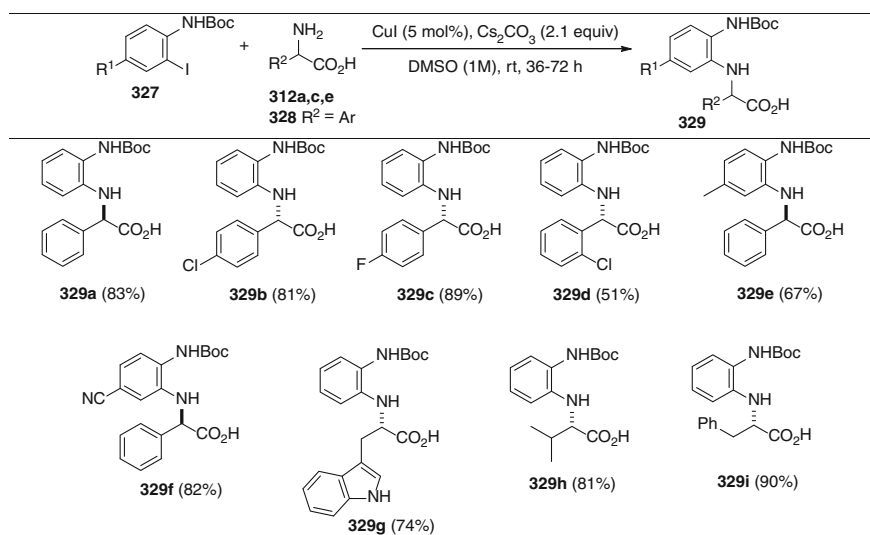
Scheme 2.58 Palladium-catalyzed cyclization of substituted bromoanilides **318**

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

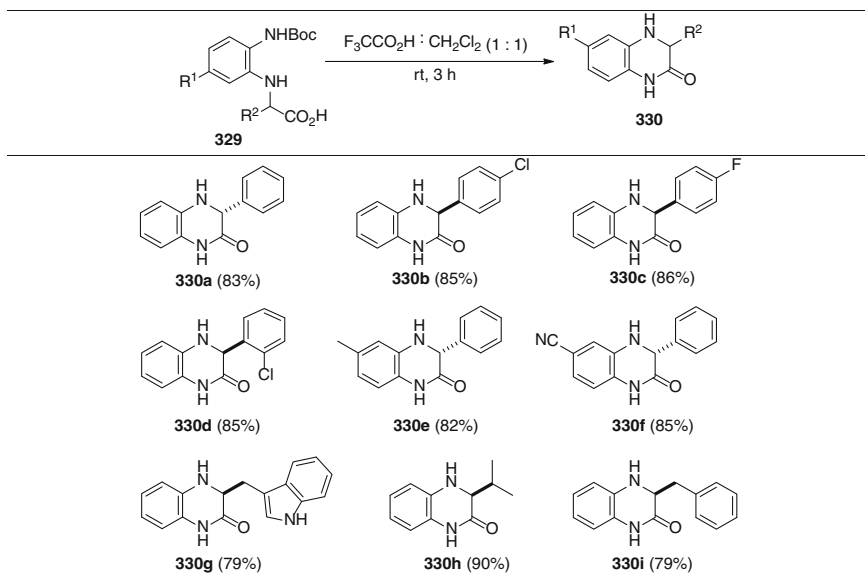


(Scheme 2.60) (Luo and De Brabander 2015). These adducts **329** were transformed into chiral 3-substituted 3,4-dihydroquinoxalin-2(1*H*)-ones **330** (Scheme 2.61) upon trifluoroacetic acid-mediated Boc deprotection/in situ cyclodehydration. Importantly, the entire two-step procedure occurs without 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



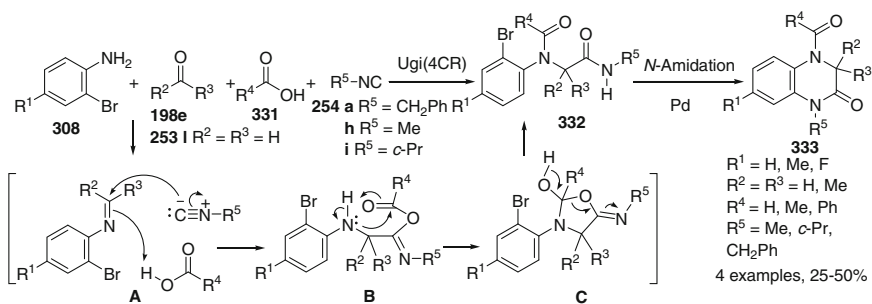
Scheme 2.60 Cross-coupling of *N*-Boc-2-iodoanilines **327** with α -amino acids **328**, **312a**, **c**, **e**. For **329a–f**, the ee was determined to be ≥ 98 % as determined by chiral stationary phase HPLC analysis using racemic products



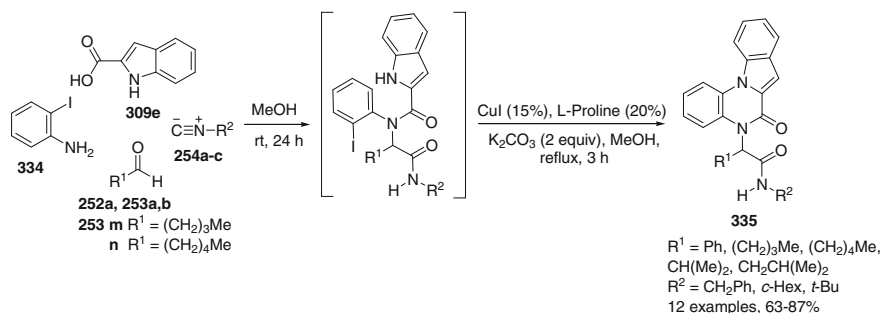
Scheme 2.61 Acid-mediated cyclization of **329** to 3-substituted-dihydroquinoxalinones **330**. For compounds **330a–c**, the ee was determined to be $\geq 98\%$ as determined by chiral stationary phase HPLC analysis using racemic products

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 $\text{Pd}_2(\text{dba})_3$, 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**



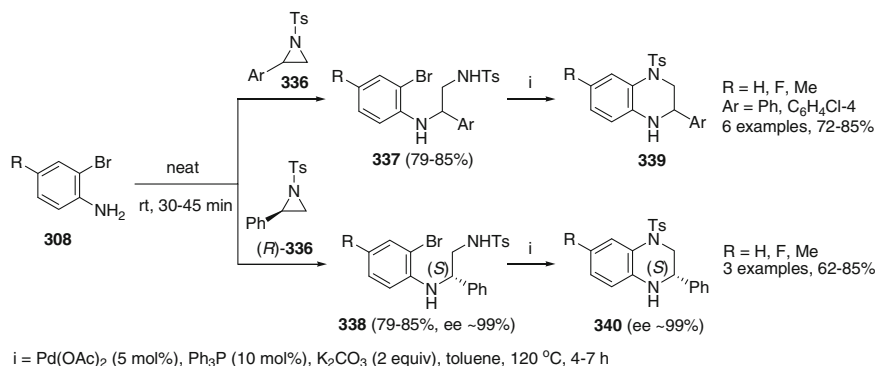
Scheme 2.63 Synthesis of indolo[1,2-*a*]quinoxalines **335** via sequential Ugi/Ullmann reaction

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).

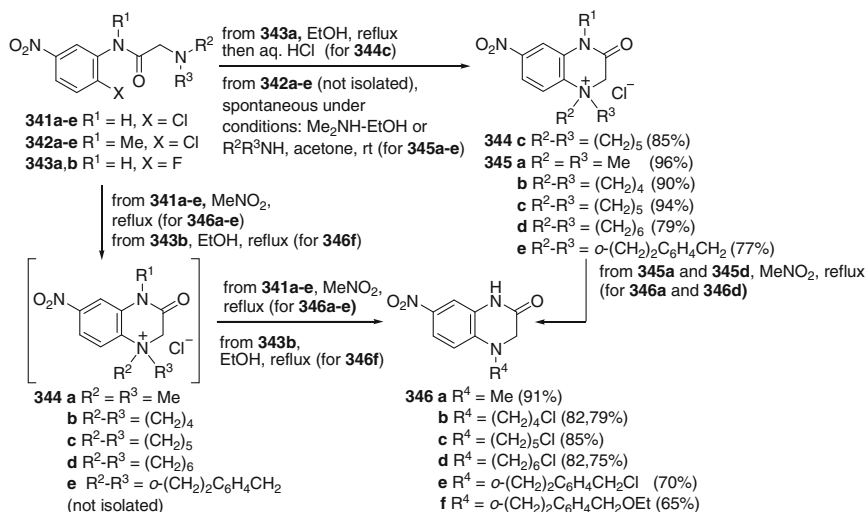
A highly regio- and stereoselective route for the synthesis of racemic **339** and nonracemic **340** substituted tetrahydroquinoxalines used the $\text{S}_{\text{N}}2$ -type ring opening of activated aziridines with 2-bromoanilines followed by the Pd-catalyzed intramolecular C–N bond formation (Scheme 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).

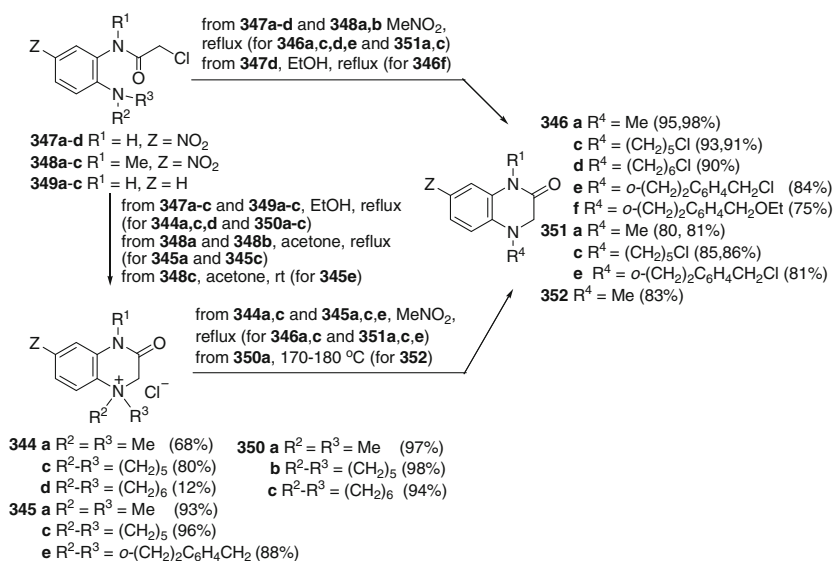
Two different, simple, and efficient methods for synthesizing quinoxaline derivatives start, respectively, from 2-dialkylamino-2'-halogeno-5'-nitroacetanilides **341–343** (Scheme 2.65) or from 2'-dialkylamino-2-halogenoacetanilides **347–349** (Scheme 2.64) (De Castro et al. 2002). Both types of acetanilide 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

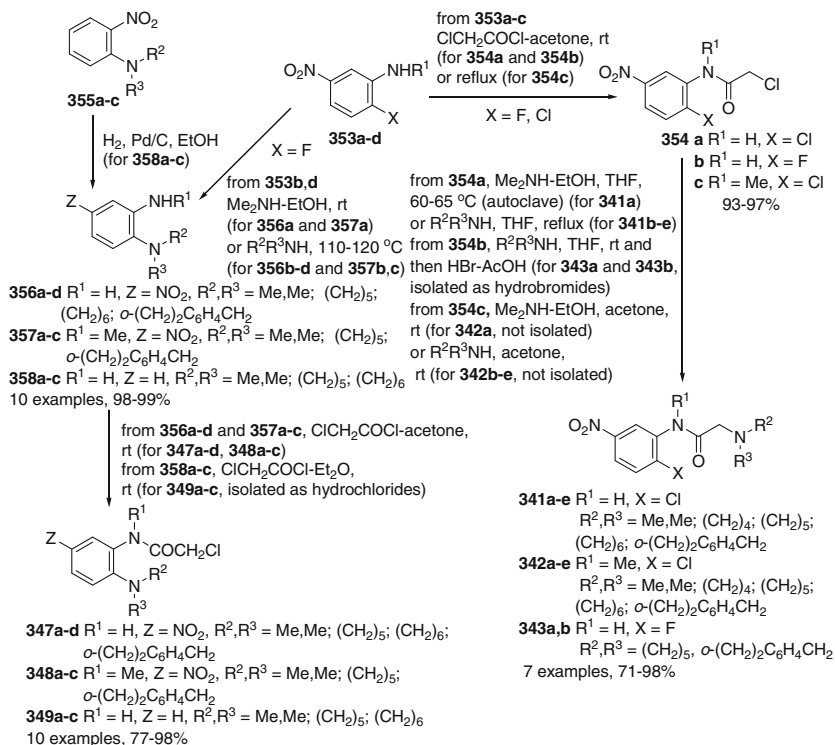


Scheme 2.65 The synthesis of quinoxaline derivatives starting from 2-dialkylamino-2'-halogeno-5'-nitroacetanilides **341**–**343**



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**.



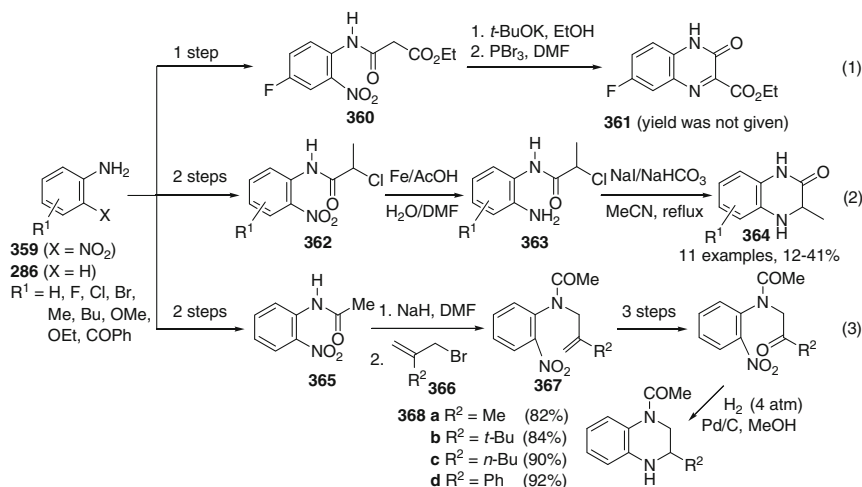
Scheme 2.67 Synthesis of 2-dialkylamino-2'-halogenoacetanilides **341–343** and 2'-dialkylamino-2-halogenoacetanilides **347–349** as precursors to quinoxalines

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.

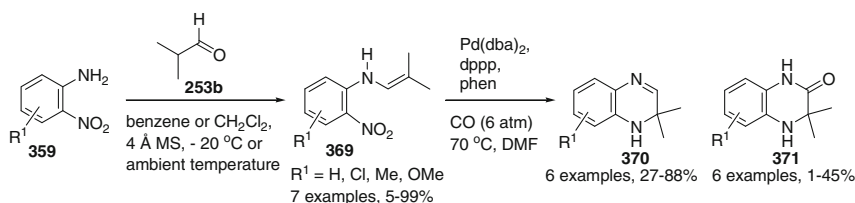
Ethyl malonyl chloride (Scheme 2.68, Eq. 1) (Takano et al. 2003), α -chloropropionyl chloride (Scheme 2.68, Eq. 2) (Li et al. 2005), allylic halides (Scheme 2.68, Eq. 3) (Bunce et al. 2003), and aliphatic aldehydes (Wallace et al. 2008) are used the



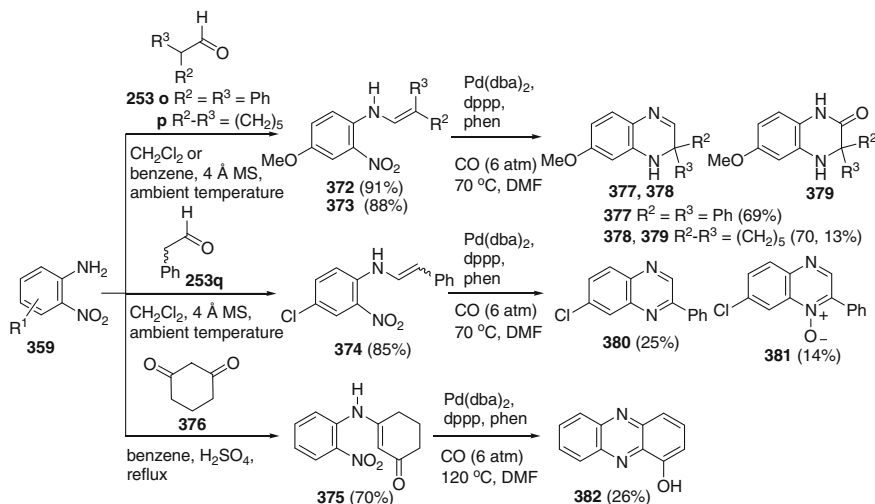
Scheme 2.68 Common strategies for the synthesis of quinoxalines starting from nitroanilines

two-carbon fragment. PBr_3 , DMF (Takano et al. 2003), Fe/AcOH (Li et al. 2005), $\text{H}_2/\text{Pd}/\text{C}$, MeOH (Bunce et al. 2003) (Scheme 2.68) and bis(dibenzylideneacetone)-palladium(0) ($\text{Pd}(\text{dba})_2$), 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**

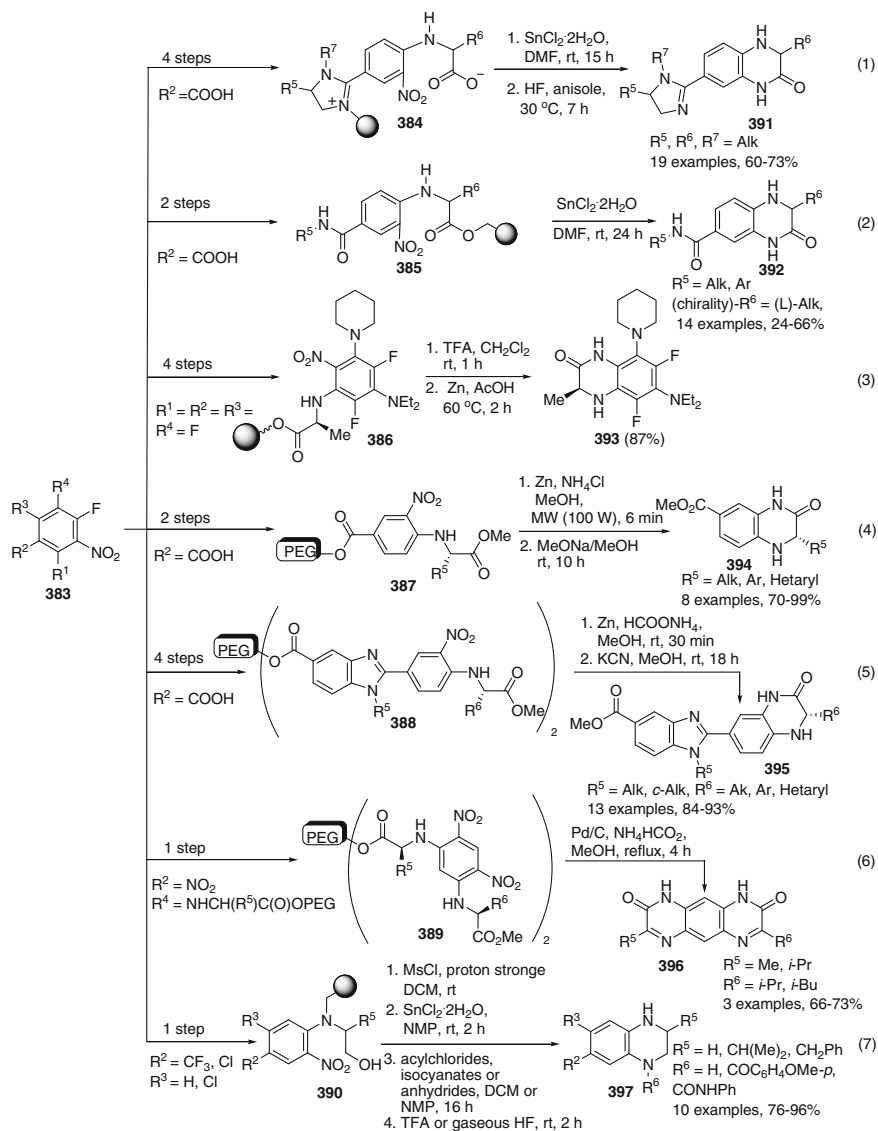


Scheme 2.70 Palladium-catalyzed synthesis of quinoxaline derivatives starting from nitroanilines and a variety of aldehydes **253o**, **p**, **q** or 1,3-cyclohexanedione **376**

2.5.5 From 2-Fluoro-1-nitrobenzenes

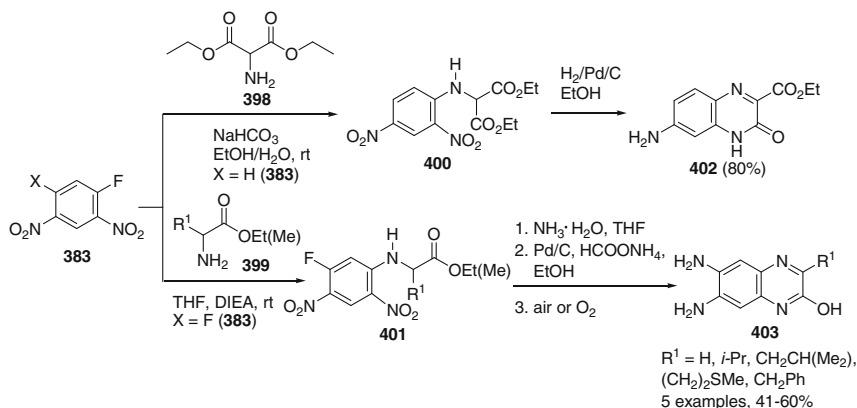
The methods of the synthesis of quinoxalines from 2-fluoro-1-nitrobenzenes involve two basic steps: (a) a nucleophilic aromatic substitution and (b) a reductive cyclization with the formation of a nitroaniline derivative. In this case, the reagent, allowing a three-atom N–C–C fragment to be introduced as a result of nucleophilic-aromatic 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

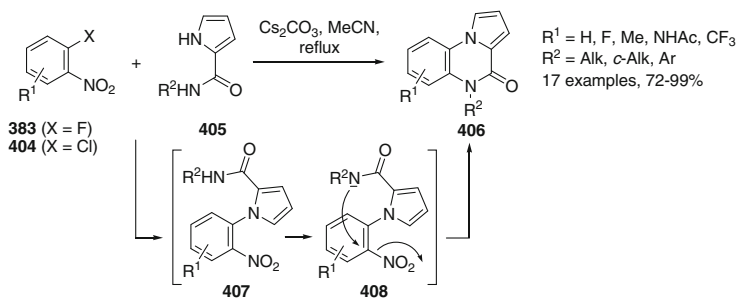


Scheme 2.71 Common strategies for the synthesis of quinoxalines starting from 2-fluoro-1-nitrobenzenes

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-quinoxalins **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

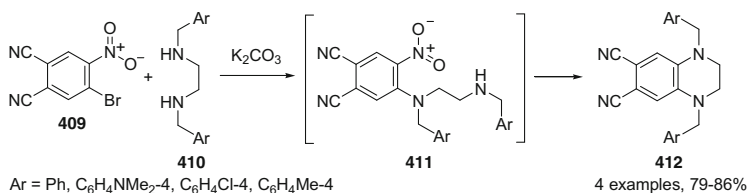
The strategy of building the pyrazine ring of the quinoxaline system is fundamentally different in the case of 4-bromo-5-nitrophthalonitrile **409**, with two nitrile groups which activate the other substituents on the benzene ring toward the nucleophilic aromatic substitution.

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).

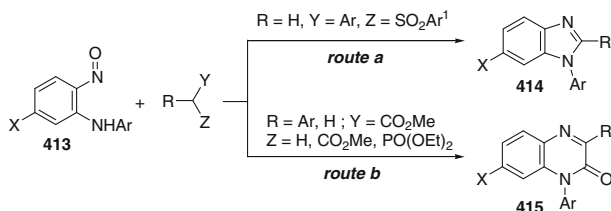
2.5.7 From *N*-Aryl-2-nitrosoanilines and Alkylated Cyanoacetic Esters

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

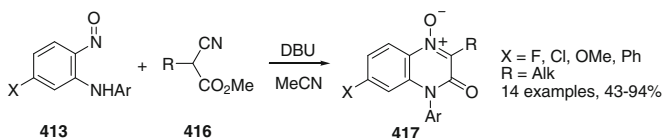


Scheme 2.74 Synthesis of *N,N'*-dialkylated tetrahydroquinoxalines **412** by the reaction of 4-bromo-5-nitrophthalonitrile **409** with secondary diamines **410**

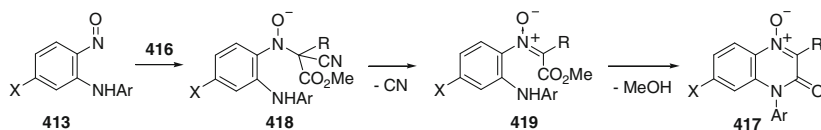


Scheme 2.75 The reaction of *N*-aryl-2-nitrosoanilines with sulfones (route *a*), acetates (route *b*) and phosphonoacetates (route *b*)

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** ($X = Cl, Ar = C_6H_3\text{-di-Me-2,6}$) 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** ($X = Cl, Ar = C_6H_3\text{-di-Me-2,6}, R = n\text{-Bu}$) 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, alkoxy, 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 nitronium **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 nitronium 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 Nelanders 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

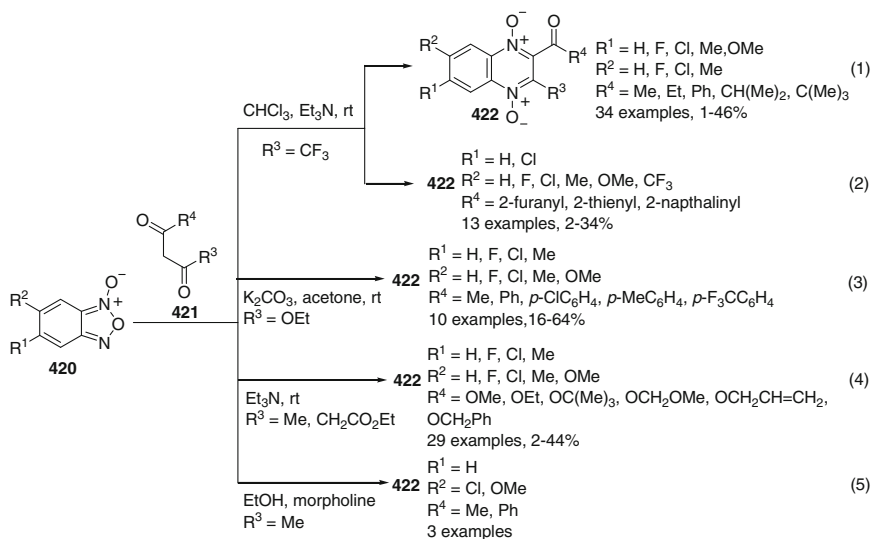
In this category, a leading place belongs to the cycloaddition reaction of benzofuroxan (benzofurazan *N*-oxide) with various suppliers of the two-carbon fragment C(2)–C(3) of the future quinoxaline (the Beirut reaction) (Laursen and Nielsen 2004). Mainly ketones (Chupakhin et al. 1999; Sun et al. 2011), 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/H₂O, H₂O, MeOH/RNH₂, SiO₂/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 benzoylacetone nitriles 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).

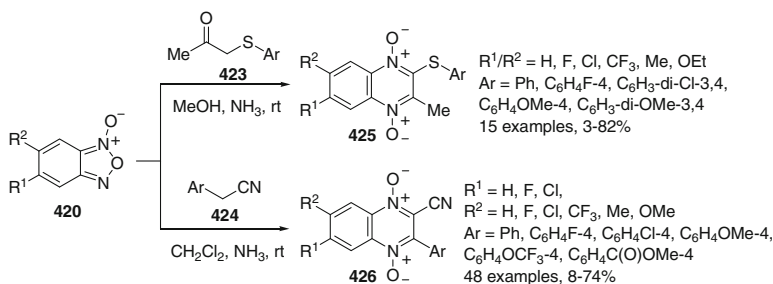
The Beirut reaction allows the introduction of any substituent at almost any position of a quinoxaline 1,4-dioxide, depending on the structures of the benzofuroxan **420** and the two-carbon unit (Scheme 2.78, Eq. 1) (Zarranz et al. 2004), (Scheme 2.78, Eq. 2) (Marin et al. 2008), (Scheme 2.78, Eq. 3) (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 acetylphenyl sulfide **423** (Carta et al. 2002, 2004) and arylacetone nitrile **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



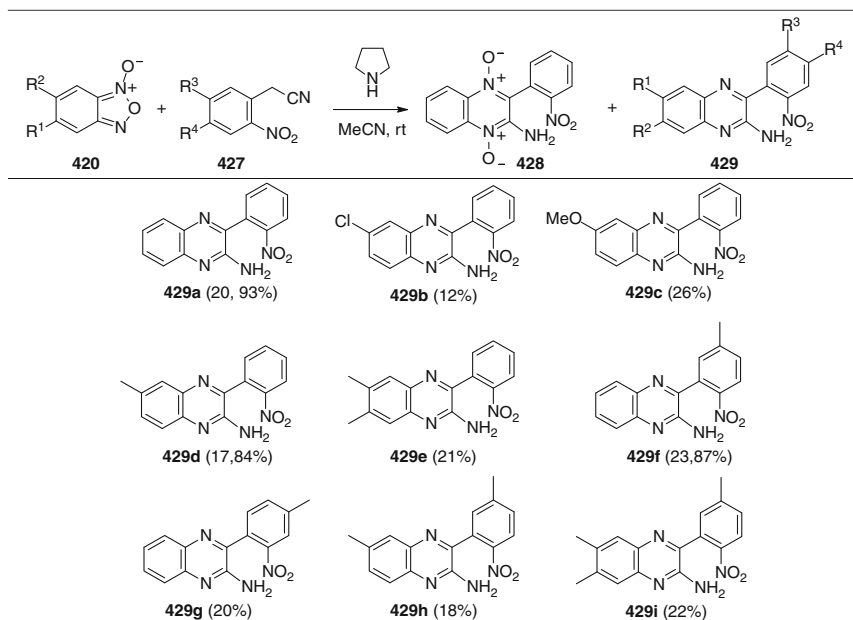
Scheme 2.78 Synthesis of 3-trifluoromethyl/alkoxy/alkyl/alkyloxycarbonyl and 2-benzoyl/aryl/alkanoyl/hetaroyl-quinoxaline 1,4-dioxide derivatives **422**



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

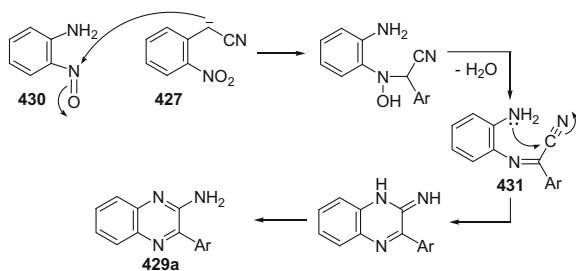
second product of this reaction, formed in almost equivalent amount, was the deoxygenated 2-amino-3-(2-nitrophenyl)quinoxalines **429** (Scheme 2.80) (Haddadin et al. 2011).

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).



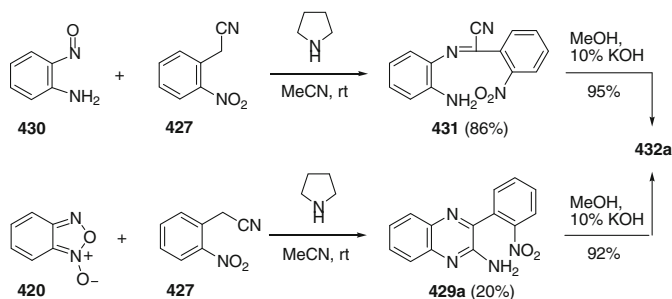
Scheme 2.80 Beirut reaction to quinoxaline derivatives

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 quinoxalino[2,3-*c*]cinnoline 5-oxides **432a–d, h**. Indeed, this type of cyclization to form cinnoline *N*-oxides is well known (Haider and

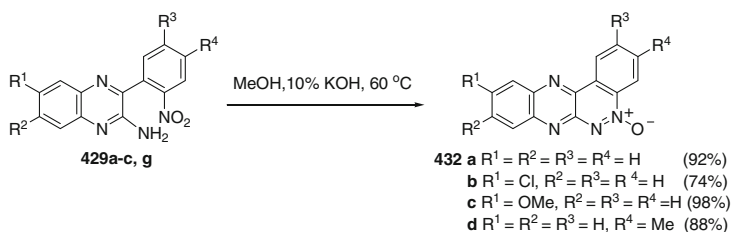


Scheme 2.82 Independent route to quinoxaline **429a**

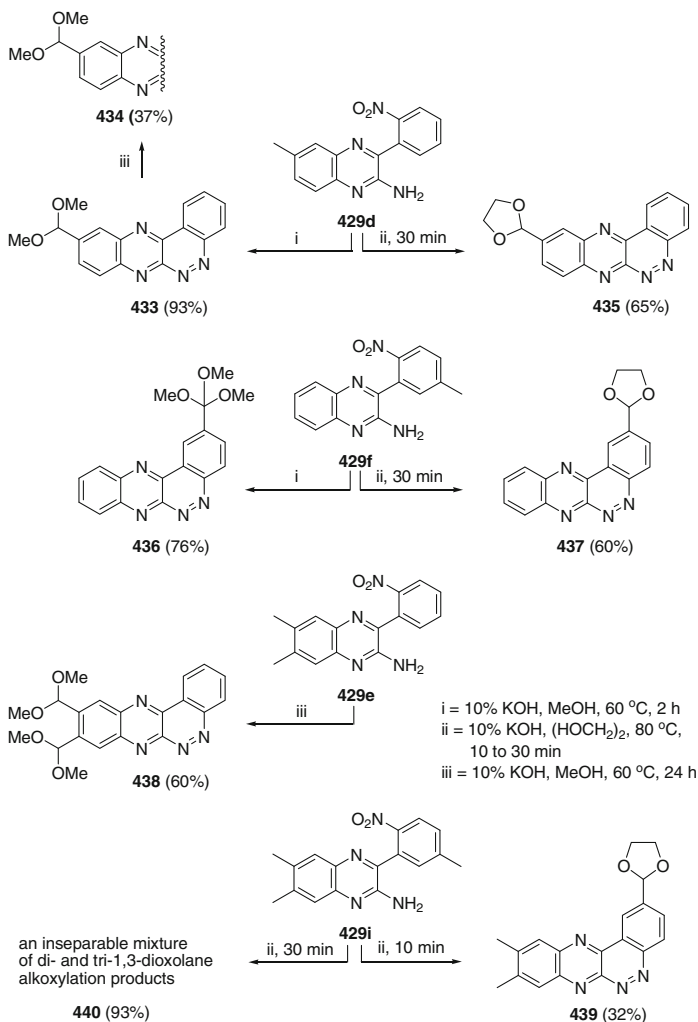
Holzer 2004). When heated methanolic KOH solutions of quinoxalines **432a–c**, **g** gave novel quinoxalino[2,3-*c*]cinnoline 5-oxides **429a–c**, **g** in high yields (80–90 %). Smith and coworkers (Shepherd and Smith 1987; Glidewell et al. 1987) have published the work on the preparation and reactions 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)



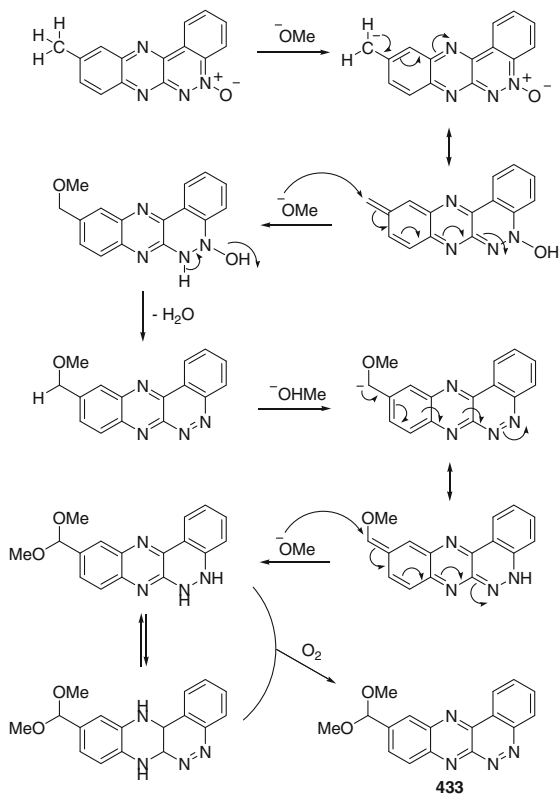
Scheme 2.83 Synthesis of quinoxalino[2,3-*c*]cinnoline 5-*N*-oxides



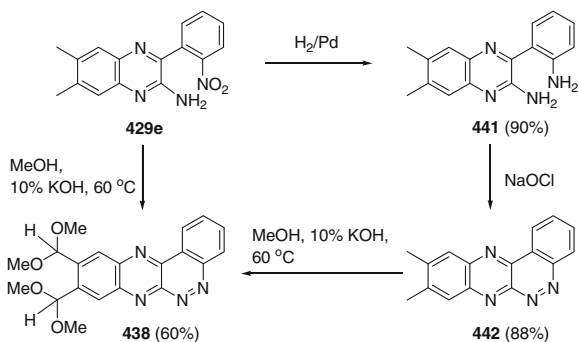
Scheme 2.84 Benzylic alkoxylation of methyl-substituted 2-aminoquinoxalines

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 (H₂/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.

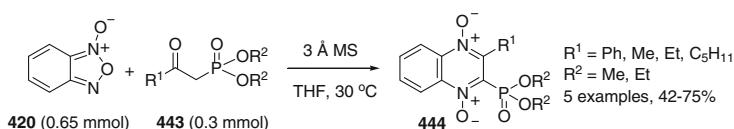
Thus, a new route for the Beirut reaction is revealed in which a number of novel 2-amino-3-(2-nitrophenyl)quinoxalines, in addition to their expected 1,4-dioxides, can be easily prepared and converted into novel quinoxalino[2,3-*c*]cinnoline 5-*N*-oxide which are rare in literature. In these investigations 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.

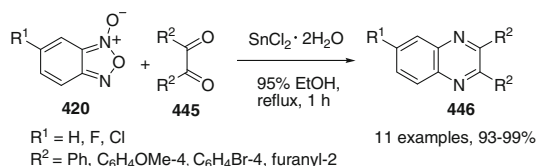
When α -dicarbonyl compounds are used instead of the usual enolizable ketones and β -carbonyl compounds, the benzofuroxans under reduction conditions (in the presence of stannous chloride $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$) behave as 1,2-DABs and form quinoxalines (Scheme 2.88) (Shi et al. 2008).

2.6.1.2 From Benzimidazole Derivatives

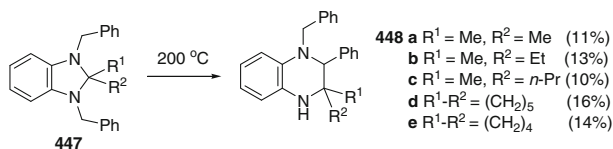
Benzimidazole, like benzofuroxan, containing two nitrogen atoms at positions 1 and 3 of the five-membered ring, can also serve as the initial reagent in quinoxaline synthesis. Thermolysis of 2,2-dialkyldihydrobenzimidazoles **447** was accompanied by their rearrangement into isomeric tetrahydroquinoxalines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



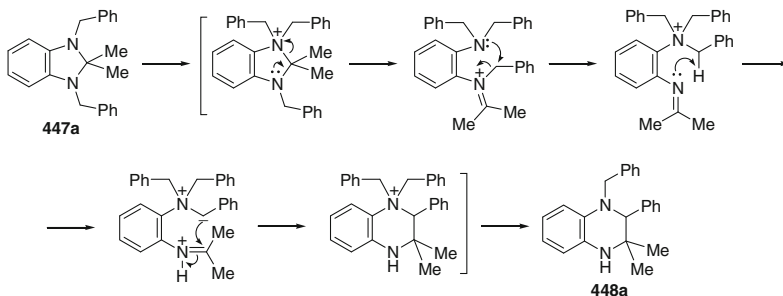
Scheme 2.87 The first successful Beirut reaction with dialkyl 2-oxopropylphosphonates



Scheme 2.88 The synthesis of quinoxalines **446** by the reaction of benzofuroxans **420** and 1,2-dicarbonyl compounds **445** mediated by $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$



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

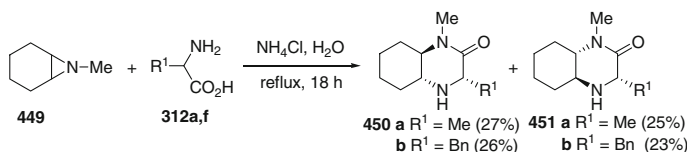
The authors proposed a possible mechanism for this reaction (shown with the dimethyl derivative as an example) (Scheme 2.90) (Reddy et al. 1996). However, they did not discuss what had happened to the molecule which provides the benzyl cation required in the first step. It should be noted that the formation 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

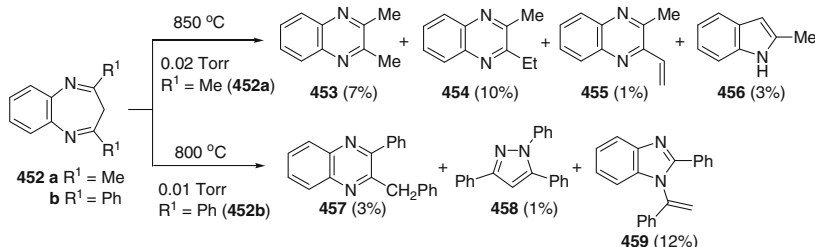
A quinoxaline-related system can emerge upon the expansion not only of a five- but also a three-membered heterocycle. New *trans*-perhydroquinoxalin-2(1*H*)-ones were prepared by the reaction of aziridines **449** with α -amino acids **312a, f** as a result of the aziridine ring cleavage and pyrazine 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



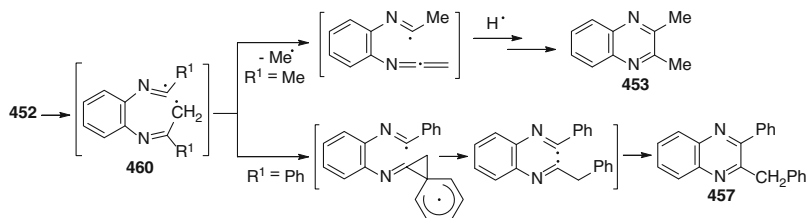
Scheme 2.92 Gas-phase pyrolysis of the 2,4-dimethyl- and 2,4-diphenyl-1,5-benzodiazepines **244a** and **244b**

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).

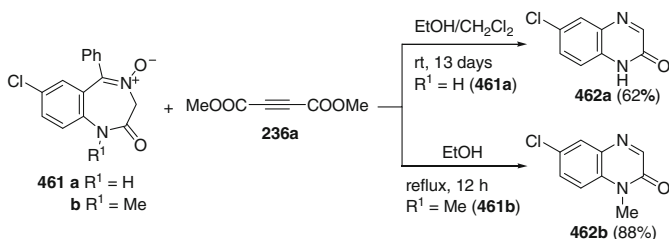
The authors suggest (Despinoy et al. 1998) that the formation of products results from homolytic cleavage of the C(2)–C(3) bond of the benzodiazepine to give an imidoyl-aza-allyl biradical pair **460**. The formation of quinoxaline **457** (3 %) requires a 1,2-phenyl shift in the aza-allyl unit, which 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 C₁ 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).

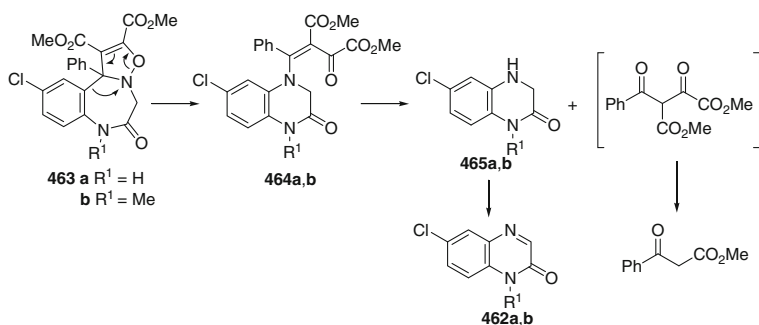
The authors assumed that under the reaction conditions, the adducts **463** were formed in the 1,3-cycloaddition, but then undergo a Beckmann-type rearrangement



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 $\rightarrow$ **464** to give quinoxalines **462**, **465** (Scheme 2.95). Under mild conditions (stirring in Et₂O and CH₂Cl₂ 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

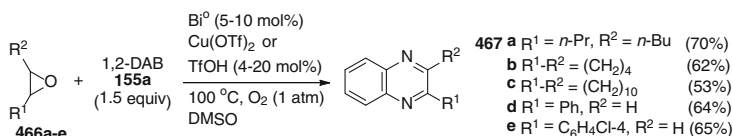
2.6.2.1 From Epoxides

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.

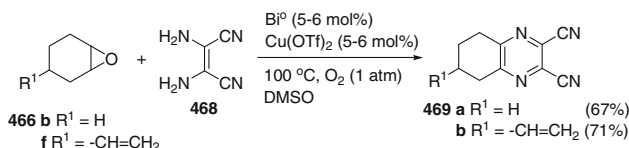
The synthesis of 2,3-disubstituted quinoxalines **467a–c** was achieved in yields of 53–70 % using 1,2-DAB **155a** and internal epoxides **466a–c** ($R^1 = n\text{-Pr}$, $R^2 = n\text{-Bu}$; $R^1\text{--}R^2 = (\text{CH}_2)_4$ and $R^1\text{--}R^2 = (\text{CH}_2)_{10}$) (Scheme 2.96). The oxidative coupling of 1,2-DAB **155a** and monosubstituted styrene oxide derivatives **466d,e** ($R^1 = \text{Ph}$, $R^2 = \text{H}$ and $R^1 = \text{C}_6\text{H}_4\text{Cl-4}$, $R^2 = \text{H}$) 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).

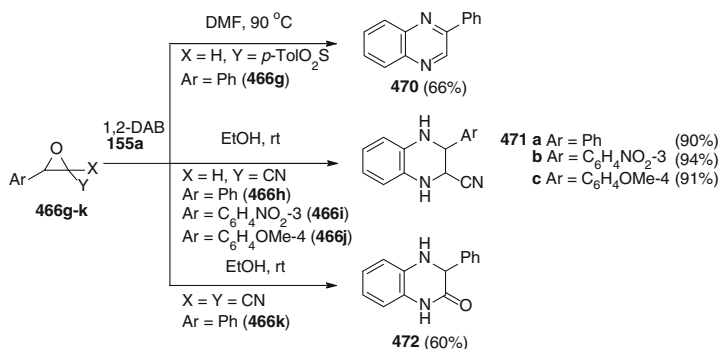
For the mechanistic aspects of this new transformation, a first oxidation of the epoxide to the corresponding α -hydroxyketone and its further oxidation to the α -diketone have been proposed in agreement with the results in this field (Antoniotti and Duñach 2001). This oxidation proceeds by the oxidative 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**

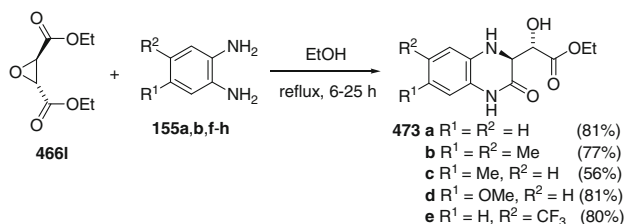
leading to the corresponding α -hydroxyketone or α -hydroxyaldehyde. In the second step, the ketol (or ketal) is oxidized to the α -diketone or to the α -ketoaldehyde intermediates according to Bi(0)/O₂ system, in a Bi(III)/Bi(0) redox process (Coin et al. 2001). The in situ α -dicarbonyl compound obtained 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** in a 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).

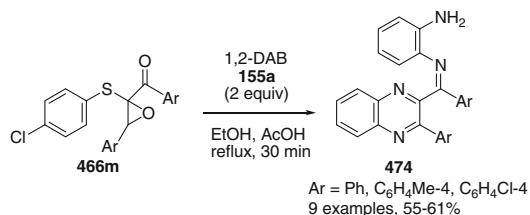
The application of this approach to 2-cyano- and 2,2-dicyano-3-aryloxiranes **466h-j** and **466k** led to 2-aryl-3-cyano- **471a-c** and 3-phenyl-2-oxo-1,2,3,4-tetrahydro- **472** quinoxalines, respectively (Scheme 2.98). They are dehydrogenated to give aromatic derivatives on heating in ethanol in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

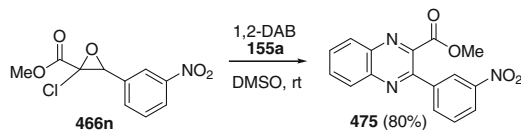


Scheme 2.100 Three-component reaction of (2-arylsulfanyl-3-aryl-2-oxiranyl)(aryl)methanones **466m** with 1,2-DAB **155a** in the presence of a catalytic amount of AcOH

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**

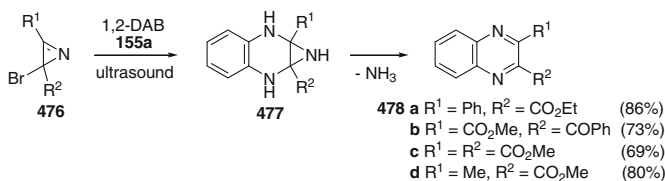
2.6.2.2 From Azirines

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** ($R^1 = \text{Ph}$, $R^2 = \text{CO}_2\text{Et}$), **476b** ($R^1 = \text{CO}_2\text{Me}$, $R^2 = \text{COPh}$), **476c** ($R^1 = R^2 = \text{CO}_2\text{Me}$), and **476d** ($R^1 = \text{Me}$, $R^2 = \text{CO}_2\text{Me}$) 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.

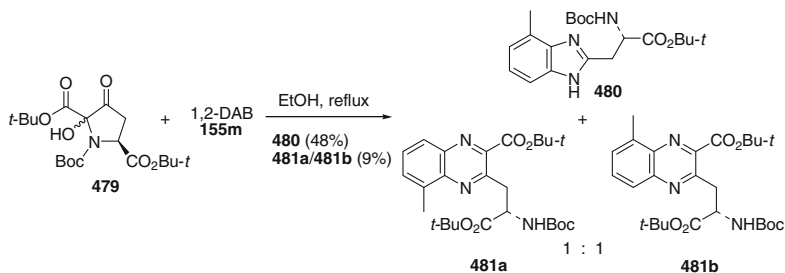
2.6.2.3 From Pyrrolidin-3-one and Piperidin-3-one

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

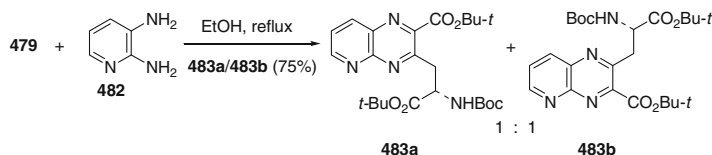


Scheme 2.103 Condensation of pyrrolidin-3-one **479** with 1,2-DAB **155m**

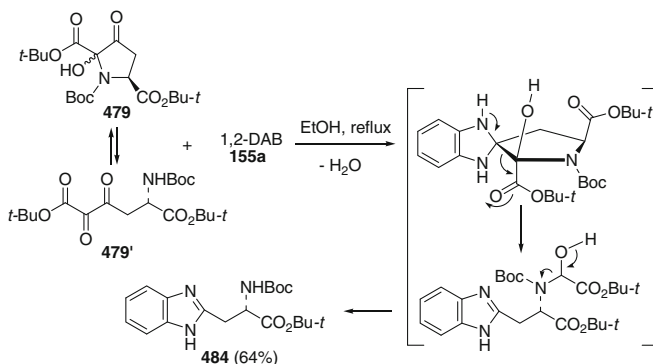
much cleaner than those above and allowed the formation of the expected quinoxaline products **483a** and **483b**, as an inseparable mixture of regioisomers in 75 % yield. No evidence of analogous benzimidazole-type products was observed (Scheme 2.104) (Adlington et al. 2001).

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).

Notwithstanding 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

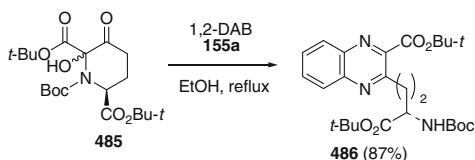


Scheme 2.104 Condensation of pyrrolidin-3-one **479** with pyridine-2,3-diamine **483**



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).

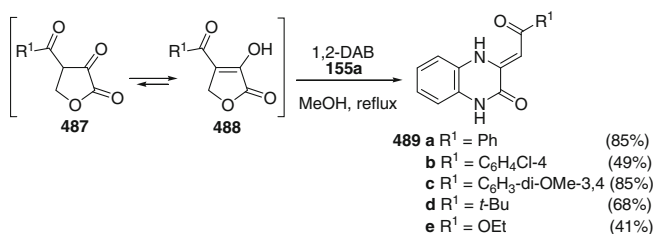
In order to compare the reactivity of piperidin-3-one **485** with its aspartate homologue **479** a reaction with 1,2-DAB **155a** was attempted. This resulted in the formation of the desired quinoxaline **486** in a very high yield (87 %), with no benzimidazole product being observed (Scheme 2.106)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

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

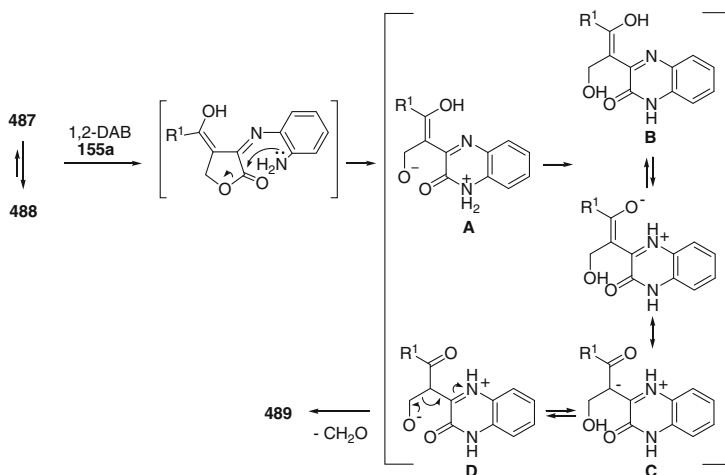
The condensation of α -keto- β -substituted γ -butyrolactones **487** (3-hydroxyfuran-2-(5*H*)-ones **488**) with 1,2-DAB **155a** results in 3-substituted 3,4-dihydroquinoxalin-2(1*H*)-ones **489** (Scheme 2.107) (Amer et al. 1983).

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

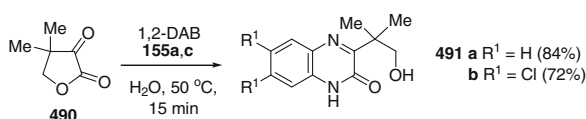


Scheme 2.107 Condensation of α -keto γ -butyrolactones **487** with 1,2-DAB **155a**



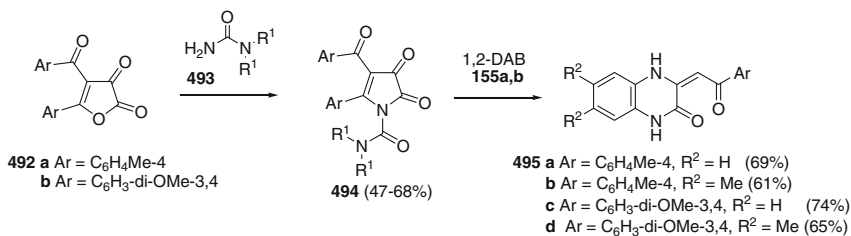
Scheme 2.108 A plausible mechanism for the formation of 3,4-dihydro-2(1H)-quinoxalinone **489** from 3-hydroxyfuran-2-(5H)-ones **487** $\rightleftharpoons$ **488**

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

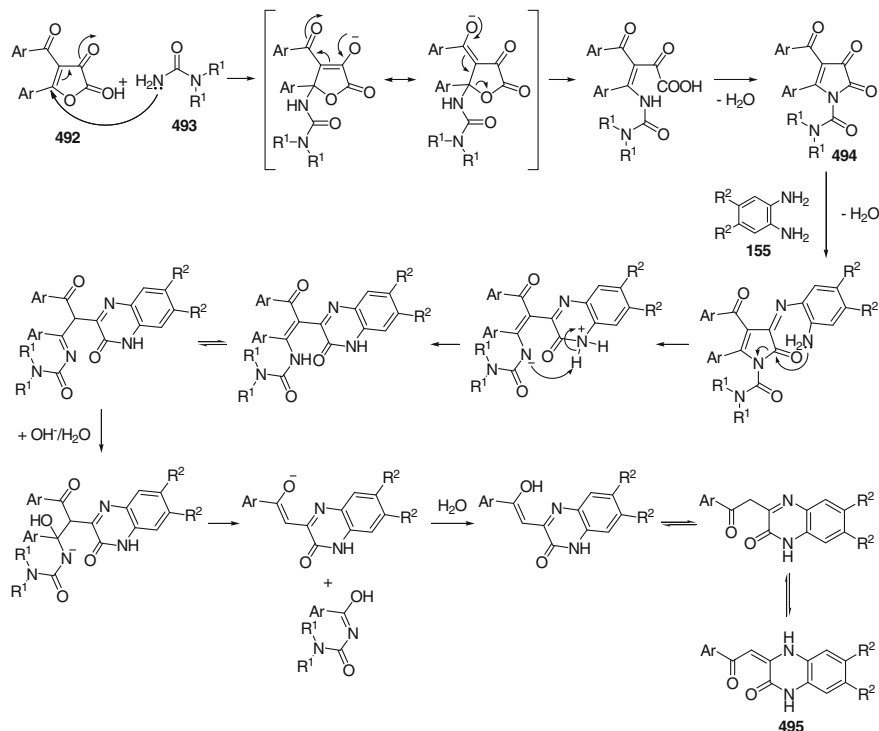


above-mentioned example, apparently due to the impossibility for the existence of different tautomeric forms such as **A**, **B**, **C**, and **D** (Scheme 2.108), due to the structural features of the original lactone **490**.

The 1H-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(1H)-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**

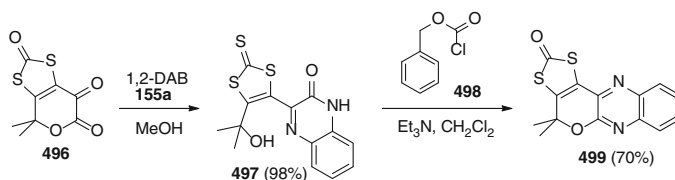


Scheme 2.111 Formation of pyrrole-2,3-diones **494** and quinoxalin-2-ones **495**

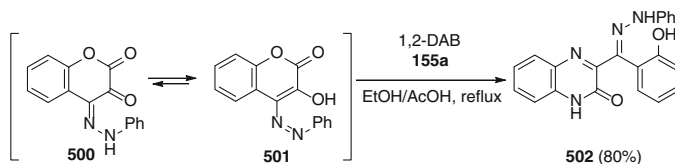
The mechanism of the formation of 1*H*-pyrrole-2,3-diones **494** involves first the Michael-type attack of nitrogen atom of NH_2 group of the urea derivative on C(5) in the furandione ring. Later, the molecule of water was eliminated and compound **494** was obtained. Nucleophilic addition of 1,2-DABs **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

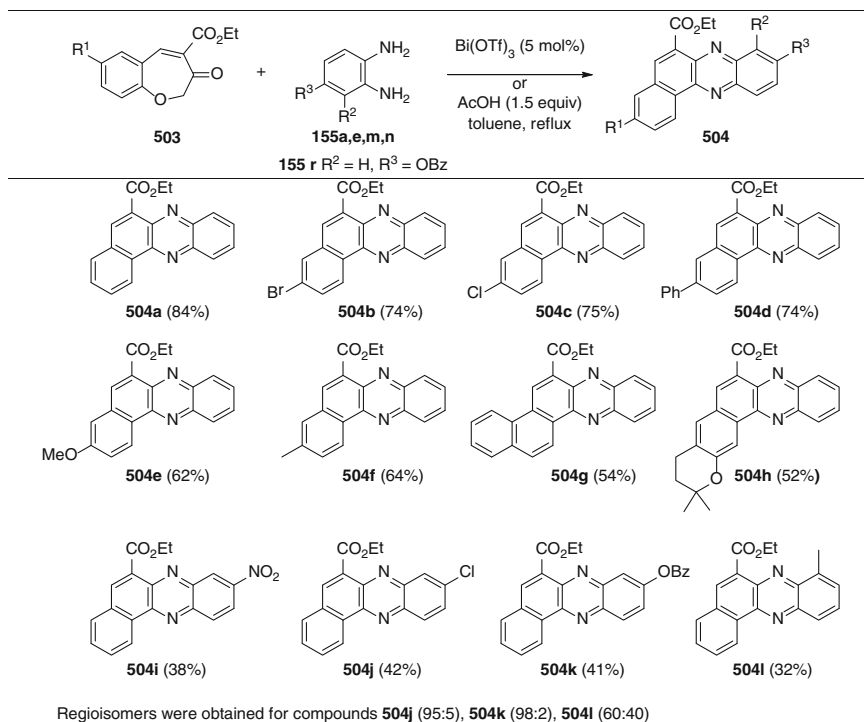
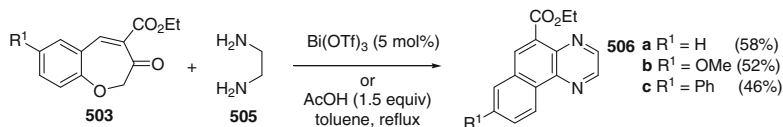
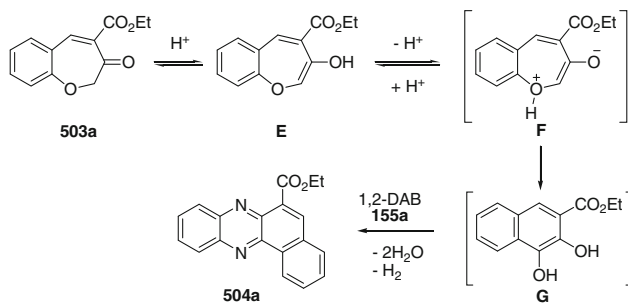
As an α -keto lactone, phenylhydrazone **500** (2*H*-chromene derivative) reacts with 1,2-DAB **155a** in a boiling EtOH/AcOH mixture, with ring cleavage giving rise to quinoxalin-2-(1*H*)-one **502** (Scheme 2.113) (Vinot et al. 1983).

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 $\text{Bi}(\text{OTf})_3$ (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** ($\text{R}^1 = \text{H}$) 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**.

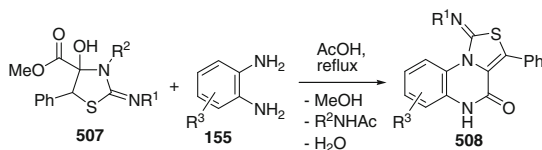
The method opens a new way for C–C, C–N, and C–O bond-formation reactions in a single-step process.

2.6.2.8 From 4-Hydroxythiazolidines

In all the above reactions, a variety of heterocyclic systems, acting as C₂ 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** (R¹ = R² = Ph)—a protected derivative of methyl phenylchloropyruvate **156e**—is used to supply the C₂ 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** (R¹ = Ph, R³ = 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 isothiurea 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**

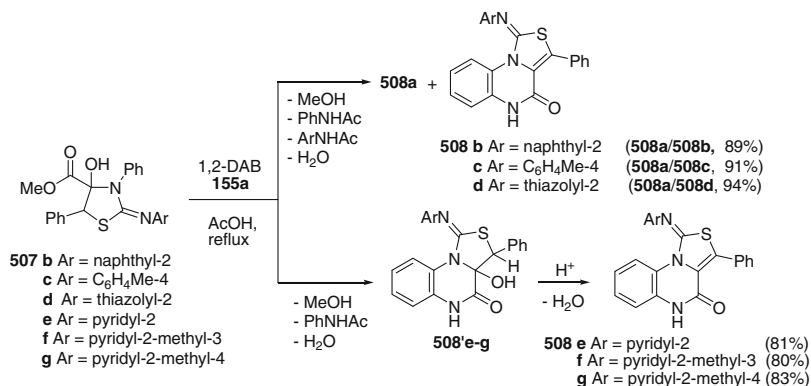
The section reveals the synthetic potential of this new reaction, not only for variously substituted thiazolo[3,4-*a*]quinoxalines but also for related new heterocyclic systems as well.

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).

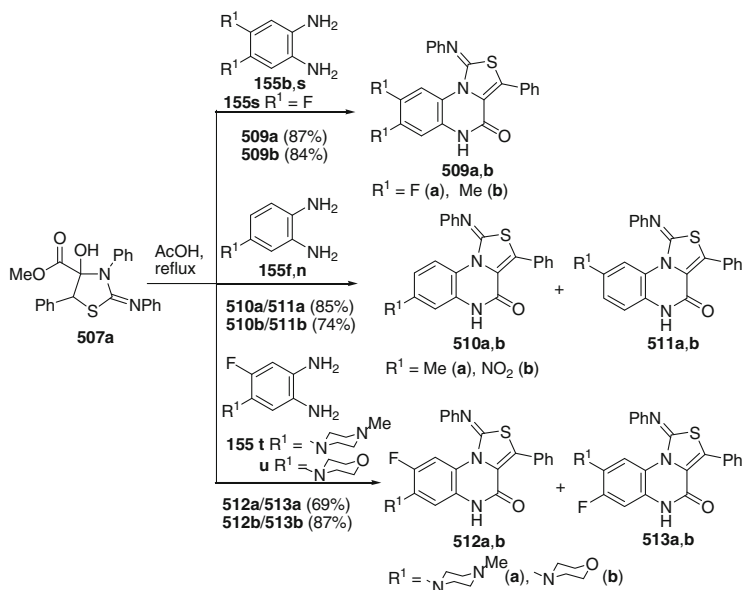
Reactions of 4-hydroxy-2-(*R*-pyridyl)iminothiazolidines **507e–g** with the non-substituted 1,2-DAB **155a** proceed with the formation of only 1-(*R*-pyridyl) iminosubstituted thiazolo[3,4-*a*]quinoxalines **508e–g** (Scheme 2.118). Thus during the condensation, the aniline and not 2-aminopyridine or 2-aminopicoline is eliminated (Mamedov et al. 2007, 2012). It may be noted that the presence of iminopyridyl and $\alpha(\gamma)$ 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 ^1H 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** with 1,2-DAB **155a**



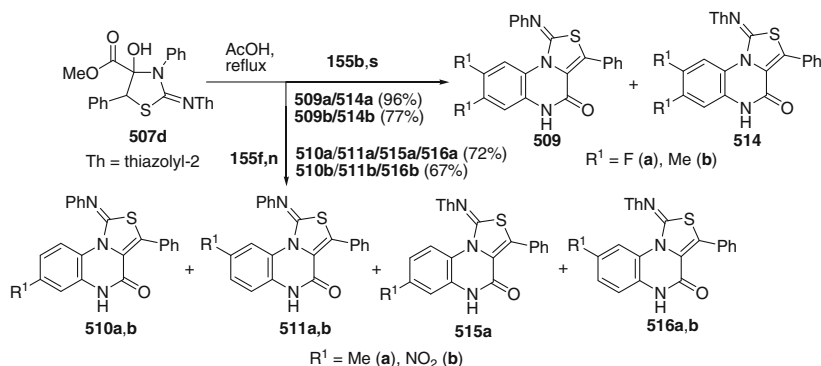
Scheme 2.119 The reactions of symmetrical 4-hydroxythiazolidine **507a** with the substituted 1,2-DABs **155b, f, n, s–u**

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**

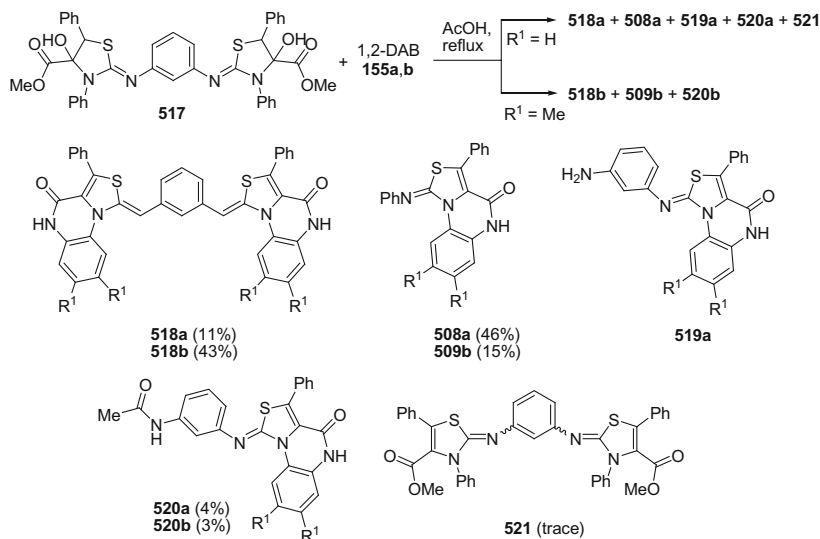
The condensation of 4-hydroxythiazolidine **507d** with 4-nitro-1,2-DAB **155n** (Scheme 2.120) affords a mixture of three out of four possible products (Mamedov et al. 2009a). This is indicated by the fact that the ^1H NMR spectrum of the crude product shows three doublets for the proton H(9) at δ 10.69, 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 ^1H spectrum, is 71:26:3.

The following should be kept in mind when carrying out the synthesis of bithiazoloquinoxalines 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).

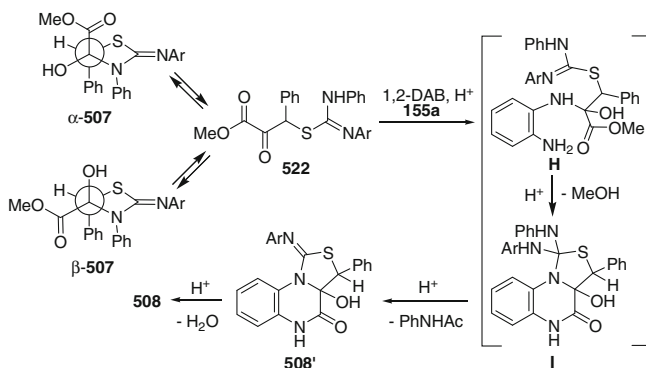
Reactions of **517** with the more basic 4,5-dimethyl-1,2-DAB **155b** generally proceed like reaction with 1,2-DAB **155a**. The exception was that bis(thiazolo[3,4-*a*]quinoxaline) **518b** was the major product, while thiazoloquinoxalines **509b** and **520b** were only by-products (Mamedov et al.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

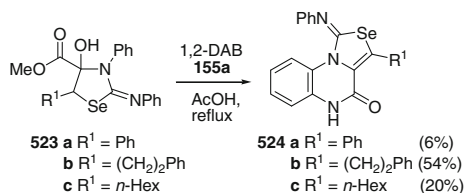
The condensation of 4-hydroxyselenazolidines **523a–c** with the non-substituted 1,2-DAB **155a** in boiling acetic acid results in the formation of the expected selenazolo[3,4-*a*]quinoxalines **524a–c**, the yields of which, in contrast to the yield ($\sim 100\%$) of the reaction with 4-hydroxythiazolidine **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).

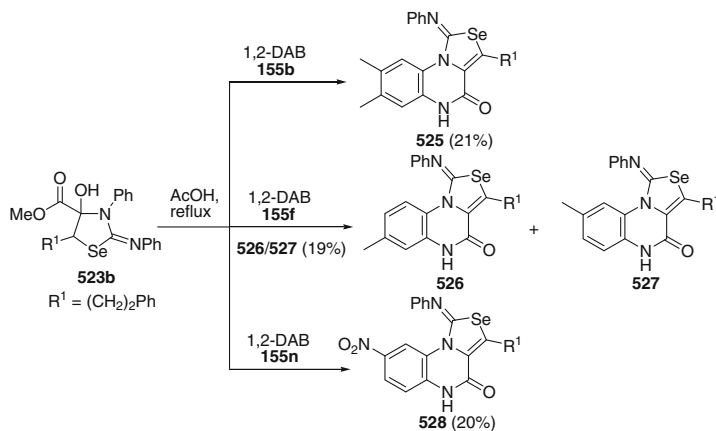
The reaction of 4-hydroxyselenazolidines **523b** with symmetrically substituted 1,2-DAB **155b** results in only one product—7,8-disubstituted selenazolo[3,4-*a*]quinoxalines **525**, with unsymmetrically substituted 1,2-DAB **155f**—a mixture of two isomeric selenazolo[3,4-*a*]quinoxalines **526** 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

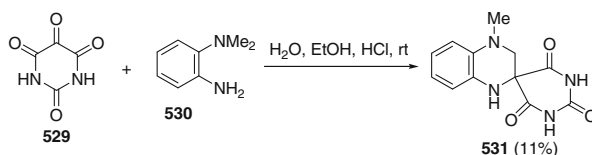
The reaction of alloxan **529** with 1,2-dimethylaminoaniline **530** in ethanol in the presence of hydrochloric acid, apart from other products, results in spiro-quinoxaline **531** in low yield (Scheme 2.125) (King and Clark-Lewis 1953).

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





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'-trioxypyrimidine) **531**

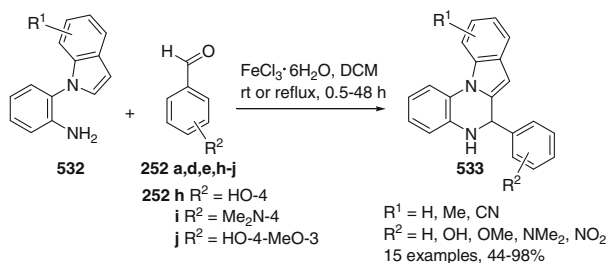
To our knowledge, this is the only case in which a 1,2-DAB derivative in the construction of the pyrazine ring of the quinoxaline system supplies five atoms (three carbon atoms and two nitrogen atoms), instead of four (two carbon and nitrogen).

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

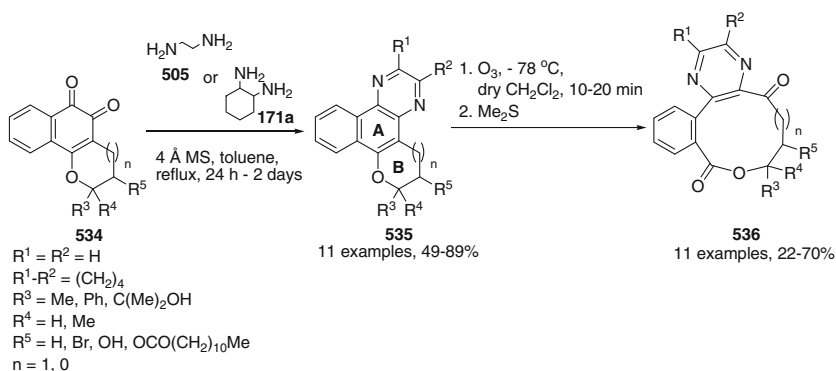
A series of new 5,6-dihydro-indolo[1,2-*a*]quinoxaline derivatives **533** has been prepared in moderate to excellent yields from 2-(indol-1-yl)benzenamines **532** with aromatic aldehydes **252a**, **d**, **e**, **h–j** by an efficient and economical iron-catalyzed Pictet–Spengler reaction (Scheme 2.126) (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-ethyldiamine **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 $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$

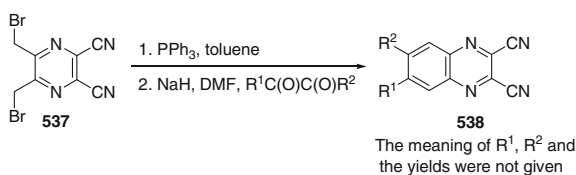


Scheme 2.127 Synthesis of 9- and 10-membered macrolactones **536**

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 $(\text{CH}_2\text{O})_n$ leading to a quinone methide intermediate, which undergoes a HDAR with styrene as dienophile (Nair and Treasa 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**

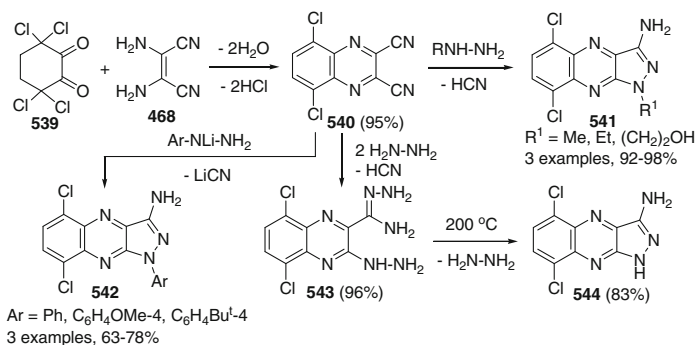
2.6.3 Synthesis of Quinoxalines from Heterocyclic Systems with a Pyrazine Ring

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 -diketone 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

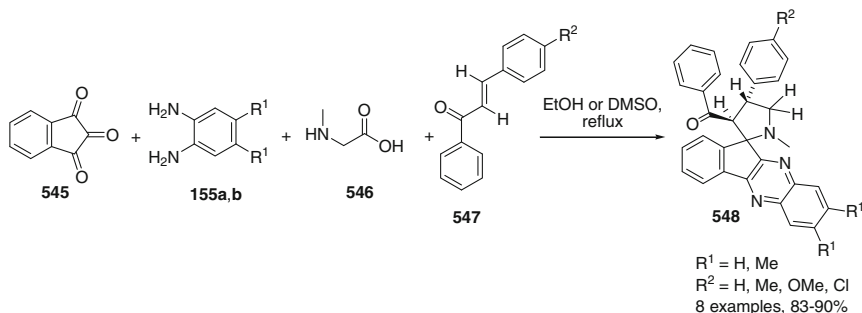
**Scheme 2.129** Synthesis and reactions of 5,8-dichloro-2,3-dicyanoquinoxaline **540** with amines and hydrazines

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.

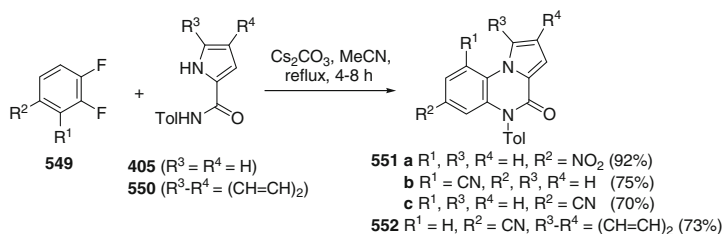
It should be pointed out that this is the only effective method for the synthesis of amino quinoxalines that can compete with any method based on the three-component condensation of 1,2-DAB, an aldehyde or ketone, and an isocyanide in the presence of a catalytic amount of *p*-TsOH, proposed and developed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