CHAPTER 1

Primary Syntheses

The primary synthesis of quinoxalines may be accomplished by cyclization of benzene substrates already bearing appropriate substituents; by cyclocondensation of benzene substrates with acyclic synthons to provide one or more of the ring atoms required to complete the pyrazine ring; by analogous processing of preformed pyrazine substrates; or by rearrangement, ring expansion/contraction, degradation, or modification of appropriate derivatives of other heterocyclic systems. Partially of even fully reduced quinoxalines may often be made by somewhat similar procedures; such cases are usually illustrated toward the end of each subsection. Examples of any pre-1977 syntheses in each category may be found from the cross-references to Simpson's volume[1013] (e.g., *H* 203) or to Cheeseman and Cookson's volume[1014] (e.g., *E* 79) that appear on some section headings; some post-1977 material on primary syntheses has been reviewed less comprehensively elsewhere.[1021–1030]

1.1. FROM A SINGLE BENZENE SUBSTRATE

Such syntheses are subdivided according to whether the N1,C8a, N1,C2, or C2,C3 bond is formed during the procedure to afford a quinoxaline.

1.1.1. By Formation of the N1,C8a Bond

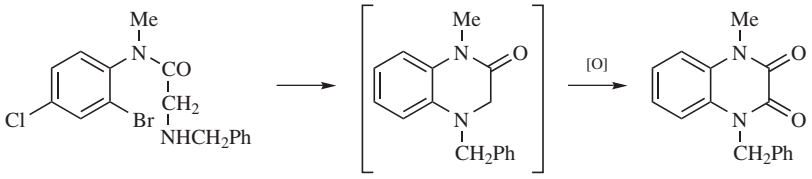
Given the relatively unreactive nature of the carbon atoms in benzene, this synthesis appears unappealing. However, several such processes have been devised, as illustrated in the following examples. All deserve further development.

By Intramolecular Aminolysis of *N*-(2-Aminoethyl)-*o*-halogenoanilines

Note: The *N*-substituent may be varied considerably; for example, the amino group may be part of a carbamoyl group.

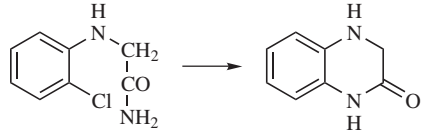
Quinoxalines: Supplement II, *Chemistry of Heterocyclic Compounds, Volume 61*, by Desmond J. Brown
ISBN 0-471-26495-4

N-(Benzylaminoacetyl)-2-bromo-4-chloro-*N*-methylaniline (**1**) gave 1-benzyl-4-methyl-2,3(1*H*,4*H*)-quinoxalinedion (**3**), probably by aerial oxidation of the dihydro intermediate (**2**) [Bu_3N, Ph_3P, $Pd(OAc)_3$, $OP(NMe_2)_3$, 110°C, CO or A (4 atm), 26 h: 68% or 38%, respectively; mechanism remains unclear].[130]



(**1**) (**2**) (**3**)

N-(Carbamoylmethyl)-*o*-chloroaniline (**4**) gave 3,4-dihydro-2(1*H*)-quinoxalinone (**5**) (''base-catalyzed cyclization'': >80%).[346]

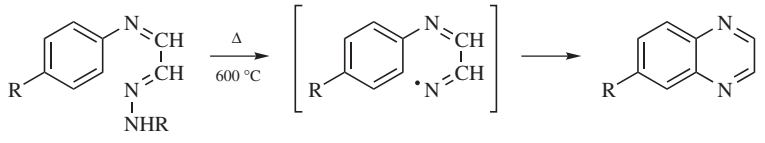


(**4**) (**5**)

Also other examples.[1063]

By Thermolysis of *N*-(Phenylhydrazonoethylidene)anilines

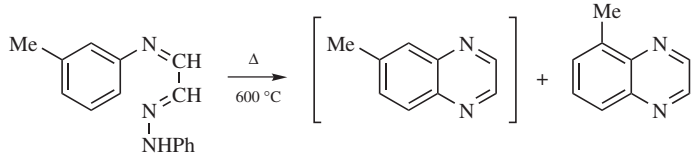
N-(Phenylhydrazonoethylidene)aniline (**6**, R = H) gave quinoxaline (**8**, R = H) via the intermediate radical (**7**) (vacuum-distilled through a tube at 600°C: 35%).[94,522]



(**6**) (**7**) (**8**)

N-(*p*-Tolylhydrazonoethylidene)-*p*-toluidine (**6**, R = Me) gave 6-methylquinoxaline (**8**, R = Me) (likewise: 36%) but the unsymmetric substrate, *N*-(phenylhydrazonoethylidene)-*m*-toluidine (**9**), gave a separable mixture of

6- (**10**) and 5-methylquinoxaline (**11**) (likewise: 15% and 23%, respectively).[528]

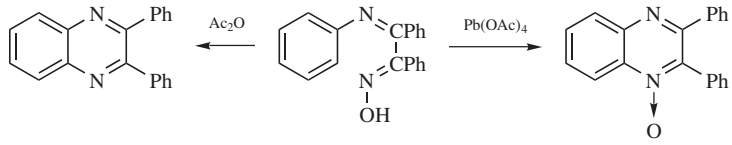


(**9**) (**10**) (**11**)

Also other examples that include observations on mechanism.[531–533]

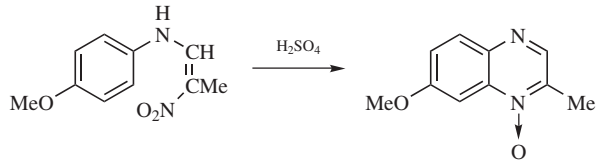
By Cyclization of *N*-(Hydroxyiminoethylidene)anilines

N-(2-Hydroxyimino-1,2-diphenylethylidene)aniline (**13**) gave 2,3-diphenylquinoxaline (**12**) [neat Ac_2O, reflux, <24 h [monitored by thin-layer chromatography (t1c)]: 57%; via the isolable acetoxyimino intermediate by a radical mechanism][1011] or 2,3-diphenylquinoxaline 1-oxide (**14**) [$Pb(OAc)_4$, CH_2Cl_2, 25°C, 1 h: 48%];[583] when unsymmetric aniline substrates were used, two isomers were formed in each case.[583,1011]



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

The somewhat analogous substrate, *p*-methoxy-*N*-(2-nitroprop-1-enyl)aniline (**15**), afforded 6-methoxy-3-methylquinoxaline 4-oxide (**16**) (98% H_2SO_4: ?%).[252]

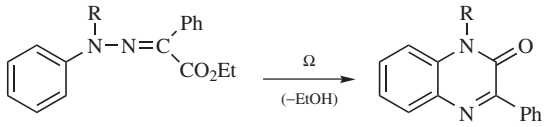


(**15**) (**16**)

By Cyclorearrangement of *N*-(Alkoxycarbonylmethylene)-*N*′-phenylhydrazines

N-(α-Ethoxycarbonylbenzylidene)-*N*′-phenylhydrazine (**17**, R = H) gave 3-phenyl-2(1*H*)-quinoxalinone (**18**, R = H) [neat polyphosphoric acid, 90°C → ~130°C

(exothermic), ~5 min (?): 20%]; *N*-(α-ethoxycarbonylethylidene)-*N*′,*N*′-diphenylhydrazine (**17**, R = Ph) likewise gave 1,3-diphenyl-2(1*H*)-quinoxalinone (**18**, R = Ph) (polyphosphoric acid, 105°C, 30 min: 20%); and several analogs were made similarly.[539]



(**17**) (**18**)

1.1.2. By Formation of the N1,C2 Bond

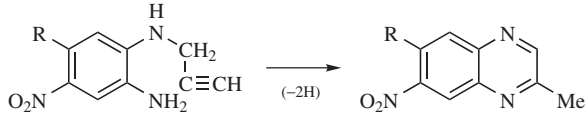
This synthesis has proved quite useful. In practice, it involves the cyclization of derivatives of *o*-(ethylamino)aniline or *o*-(ethylamino)nitrobenzene: available examples fit naturally into three broad categories outlined in the following subsections.

1.1.2.1. Cyclization of o-(Ethylamino)aniline Derivatives

The cyclization of several types of these derivatives is illustrated in the following examples.

From *o*-(Alk-2-ynylamino)anilines

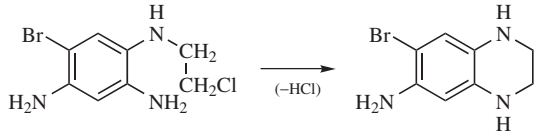
3-Nitro-6-(prop-2-ynylamino)aniline (**19**, R = H) gave 2-methyl-7-nitroquinoxaline (**20**, R = H)[$(MeCN)_4CuBF_4$, PhMe, 85°C, 20 h: 75%; aerial oxidation?]; 2,6-dimethyl-7-nitroquinoxaline (**20**, R = Me) was made similarly (78%).[640]



(**19**) (**20**)

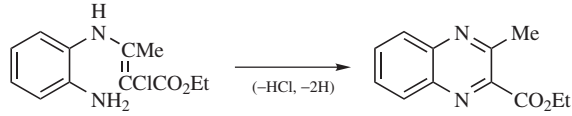
From *o*-(2-Halogenoethylamino)anilines or the Like

4-Bromo-6-(2-chloroethylamino)-1,3-benzenediamine (**21**) gave 7-bromo-1,2,3,4-tetrahydro-6-quinoxalinamine (**22**) (Na_2CO_3, Me_2NCHO, reflux, 1 h: 85%).[39]



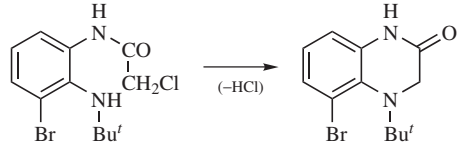
(**21**) (**22**)

o-(2-Chloro-2-ethoxycarbonyl-1-methylvinyl)aniline (**23**) gave ethyl 3-methyl-2-quinoxalinecarboxylate (**24**) (Et_3N, xylene, or Me_2NCHO, reflux, 4 h: 57%; presumably, aerial oxidation was involved).[764]



(**23**) (**24**)

2-Bromo-*N*-*tert*-butyl-6-(2-chloroacetamido)aniline (**25**) gave 5-bromo-4-*tert*-butyl-3,4-dihydro-2(1*H*)-quinoxalinone (**26**) ($EtPr^i_2N$, NaI, MeCN, reflux, 22 h: 79%).[732]

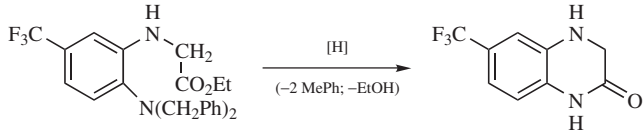


(**25**) (**26**)

Also other examples.[181,322,390,635,997]

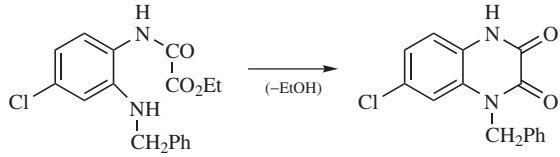
From *o*-[(Alkoxycarbonylmethyl)amino]anilines or the Like

N,*N*-Dibenzyl-2-(ethoxycarbonylmethyl)amino-4-(trifluoromethyl)aniline (**27**) underwent reductive debenzylation and spontaneous cyclization to 6-trifluoromethyl-3,4-dihydro-2(1*H*)-quinoxalinone (**28**) [$Pd(OH)_2$/C, EtOH, H_2 (3 atm), 3 days: 97%].[740]



(**27**) (**28**)

N-Benzyl-3-chloro-6-(ethoxalylamino)aniline (**29**) gave 1-benzyl-7-chloro-2,3(1*H*,4*H*)-quinoxalinedione (**30**) (EtONa/EtOH or HCl/EtOH, 20°C, ? h: >95%).[17]

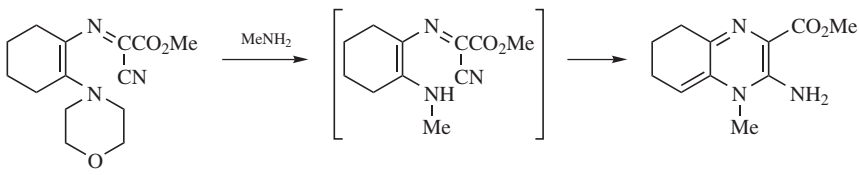


(**29**) (**30**)

Also other examples.[998,1066,1104]

From *o*-[(Cyanomethyl)amino]aniline Analogs

1-(α-Cyano-α-methoxycarbonylmethyleneamino)-2-methylaminocyclohexene (**32**), made in situ by transamination of the 2-morpholino analog (**31**), cyclized spontaneously to a reduced bicyclic product formulated confidently as methyl 3-amino-4-methyl-4,6,7,8-tetrahydro-2-quinoxalinecarboxylate (**33**) [$MeNH_2$, MeOH (?), 20°C, ? h: 84%];[50,655] the 4-(2-methoxyethyl) (90%) and other analogs were made similarly.[50,655] (See also Section 1.2.1.)



(**31**) (**32**) (**33**)

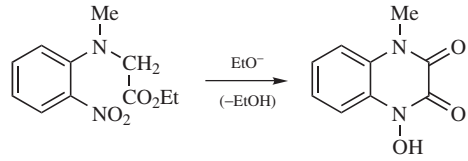
1.1.2.2. Direct Cyclization of o-(Ethylamino)nitrobenzene Derivatives (E 33)

Such direct cyclizations usually occur in basic media to afford quinoxaline *N*-oxides. For success, C2 in the ethyl group needs to be a carbonyl entity or to be suitably activated. The following examples illustrate this valuable route to such *N*-oxides (and thence to quinoxalines; see Section 4.6.2.1).

From *o*-[(Alkoxycarbonylmethyl)amino]nitrobenzenes

o-(*N*-Ethoxycarbonylmethyl-*N*-methylamino)nitrobenzene (**34**) gave 1-hydroxy-4-methyl-2,3(1*H*,4*H*)-quinoxalinedione (**35**) (EtONa, EtOH, <5°C, 15 h:

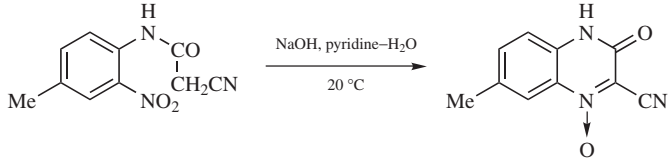
44%);[645,677] analogs were made similarly (or in the presence of other bases) in mediocre yield.[542,556,648,677]



(**34**) (**35**)

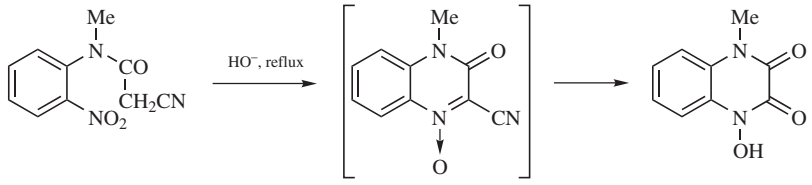
From *o*-Acetamidonitrobenzene

1-(2-Cyanoacetamido)-4-methyl-2-nitrobenzene (**36**) gave 7-methyl-3-oxo-3,4-dihydro-2-quinoxalinecarbonitrile 1-oxide (**37**) (NaOH, pyridine-H_2O, 20°C, 30 min: ? %).[98]



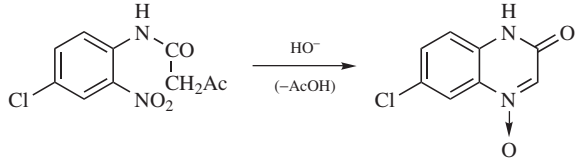
(**36**) (**37**)

In contrast, *o*-(2-cyano-*N*-methylacetamido)nitrobenzene (**38**) gave 1-hydroxy-4-methyl-2,3(1*H*,4*H*)-quinoxalinedione (**40**), presumably by hydrolysis of the intermediate carbonitrile (**39**) (NaOH, H_2O, reflux, 30 min: 53%; or EtONa, EtOH, reflux, 30 min, aqueous workup: 69%).[542]



(**38**) (**39**) (**40**)

1-(Acetoacetylamino)-4-chloro-2-nitrobenzene (**41**) gave 6-chloro-2(1*H*)-quinoxalinone 4-oxide (**42**) (KOH, H_2O, 60°C, 20 min: 86%);[391] analogs likewise.[391,413]

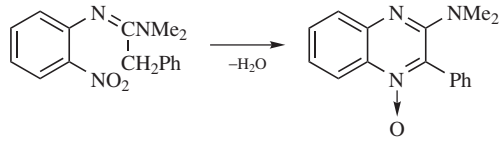


(**41**) (**42**)

Also other examples.[742]

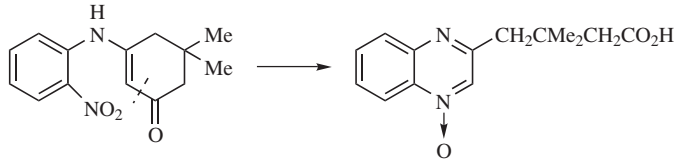
From *o*-(Ethylideneamino)nitrobenzenes

o-(1-Dimethylamino-2-phenylethylideneamino)nitrobenzene (**43**) gave 2-dimethylamino-3-phenylquinoxaline 4-oxide (**44**) (EtONa, EtOH, 20°C, 30 min: 65%); several analogs similarly.[579]



(**43**) (**44**)

o-(5,5-Dimethyl-3-oxocyclohex-1-en-1-yl)nitrobenzene (**45**) gave 2-(3-carboxy-2,2-dimethylpropyl)quinoxaline 4-oxide (**46**), probably via ring fission of a tricyclic intermediate (NaOH, Bu^{t}OH, reflux, 1 h: 92%); several analogs similarly.[568]



(**45**) (**46**)

Also somewhat less practical examples.[528,820]

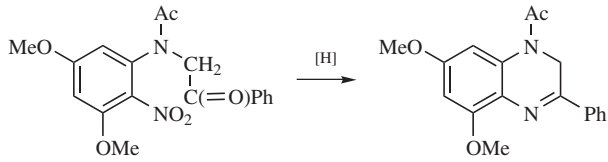
1.1.2.3. Reductive Cyclization of o-(Ethylamino)nitrobenzene Derivatives

Catalytic hydrogenation or chemical reduction with concomitant cyclization has been used to convert several types of such nitro substrates into a variety of quinoxalines. The following examples, classified according to type of substrate, illustrate the possibilities available.

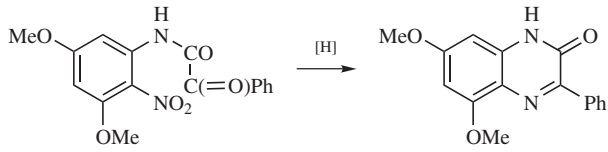
From *o*-[(Acylmethyl(amino]nitrobenzenes and the Like

1-(*N*-Acetyl-*N*-phenethylamino)-3,5-dimethoxy-2-nitrobenzene (**47**) gave 1-acetyl-5,7-dimethoxy-3-phenyl-1,2-dihydroquinoxaline (**48**) ($Na_2S_2O_4$, H_2O–MeOH, reflux, 30 min: 65%);[486] by a similar procedure, 1,3-dimethoxy-4-

nitro-5-phenyloxalylaminobenzene (**49**) gave 5,7-dimethoxy-3-phenyl-2(1*H*)-quinoxalinone (**50**) (72%).[486]

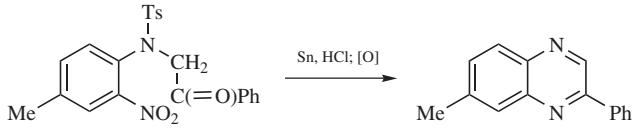


(**47**) (**48**)



(**49**) (**50**)

1-(*N*-Phenacyl-*N*-tosylamino)-4-methyl-2-nitrobenzene (**51**) gave 6-methyl-3-phenylquinoxaline (**52**) ($SnCl_2$, HCl–AcOH, 60°C, 90 min: 54%; aromatization by aerial oxidation during workup?).[530]

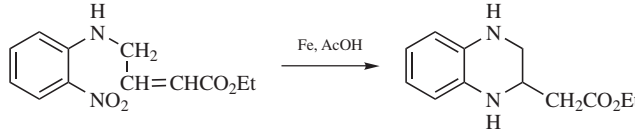


(**51**) (**52**)

1-(*N*-Acetonyl-*N*-benzenesulfonylamino)-4-fluoro-2-nitrobenzene somewhat similarly gave 6-fluoro-3-methylquinoxaline (Raney Ni, H_2, AcOEt, 20°C, 5 min: 22%; aerial aromatization?).[5]

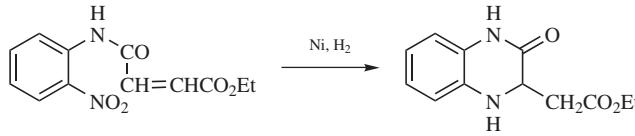
From *o*-(2-Alkylideneethylamino)nitrobenzenes or the Like

o-(3-Ethoxycarbonylallylamino)nitrobenzene (**53**) gave 2-ethoxycarbonylmethyl-1,2,3,4-tetrahydroquinoxaline (**54**) (Fe, AcOH, N_2, reflux, 30 min: 89%); also a homolog likewise.[329]



(**53**) (**54**)

O-(3-Ethoxycarbonylacrylamido)nitrobenzene (**55**) gave 3-ethoxycarbonylmethyl-3,4-dihydro-2(1*H*)-quinoxalinone (**56**) [Raney Ni, H_2 (3 atm), MeOH, 20°C, 2 h: 78%]; also analogs.[428]

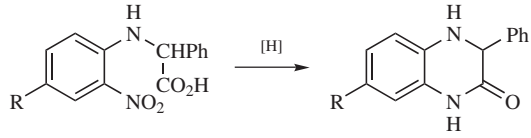


(**55**) (**56**)

Also other examples.[319]

From *o*-[(Carboxymethyl)amino]nitrobenzenes

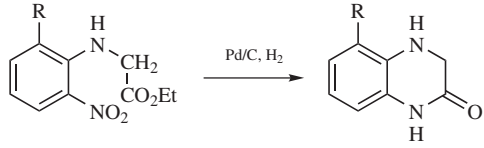
1-Acetyl-4-(α-carboxybenzylamino)-3-nitrobenzene (**57**, R = Ac) gave 7-acetyl-3-phenyl-3,4-dihydro-2(1*H*)-quinoxalinone (**58**, R = Ac) [Pd/C, H_2 (3 atm), EtOH, 20°C, 30 min: 64%];[885] 7-fluoromethyl-3-phenyl-3,4-dihydro-2(1*H*)-quinoxalinone (**58**, $R = CF_3$) was made similarly from substrate (**57**, $R = CF_3$) [Pd/C, H_2 (1 atm), EtOH, 18°C, 1 h: 57%].[840]



(**57**) (**58**)

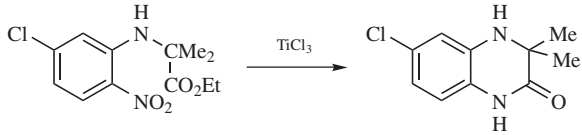
From *o*-[(Alkoxycarbonylmethyl)amino]nitrobenzenes or the Like

o-[(Ethoxycarbonylmethyl)amino]nitrobenzene (**59**, R = H) gave 3,4-dihydro-2(1*H*)-quinoxalinone (**60**, R = H) [Pd/C, H_2 (3 atm), MeOH, 20°C, 90 min: 88%];[724] 1-[(ethoxycarbonylmethyl)amino]-2-methyl-6-nitrobenzene (**59**, R = Me) gave 5-methyl-3,4-dihydro-2(1*H*)-quinoxalinone (**60**, R = Me) [Pd/C, H_2 (3 atm), EtOH, 20°C, 3.5 h: 93%; note that the product is incorrectly named in the original paper].[1042]



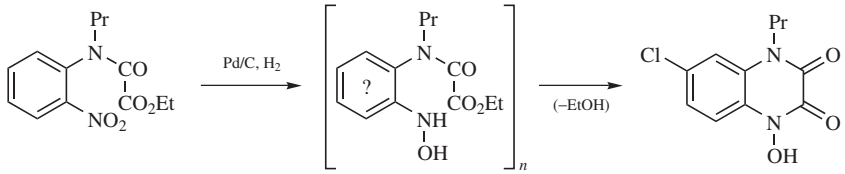
(**59**) (**60**)

1-Chloro-3-[(1-ethoxycarbonyl-1-methylethyl)amino]-4-nitrobenzene (**61**) gave 6-chloro-3,3-dimethyl-3,4-dihydro-2(1*H*)-quinoxalinone (**62**) ($TiCl_3$, AcONa, HeO–MeOH, 20°C, 2.5 h: >95%).[1042]

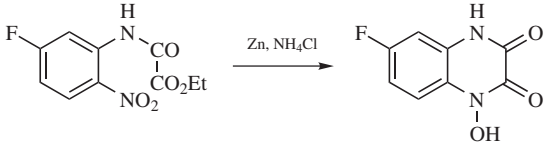


(**61**) (**62**)

In contrast, *o*-(*N*-ethoxalyl-*N*-propylamino)nitrobenzene (**63**) gave 1-hydroxy-4-propyl-2,3(1*H*,4*H*)-quinoxalinedione (**65**), perhaps via the partly reduced substrate (**64**) [Pd/C, H_2 (3 atm), Me_2NCHO, 3 h: 85%);[713] likewise, 1-(ethoxalylamino)-3-fluoro-6-nitrobenzene (**66**) gave 6-fluoro-1-hydroxy-2,3(1*H*,4*H*)-quinoxalinedione (**67**) (Zn, NH_4Cl, H_2O–Me_2NCHO, <35°C, 57%) and the 4-hydroxy isomer was made in even better yield using hydrogenation over Ir/C.[730]



(**63**) (**64**) (**65**)



(**66**) (**67**)

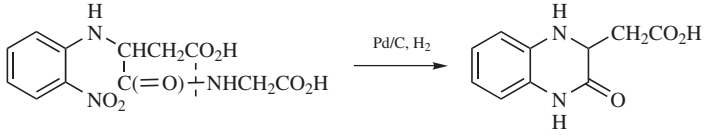
Also many other examples,[12,16,606,681,708,880,1010] including some solid-phase syntheses.[176,187]

From *o*-[(Carbamoylmethyl)amino]nitrobenzene Derivatives

Note: Several complicated but interesting examples of this cyclization have been reported; all involve loss of a substituted-amino portion of the carbamoyl grouping.

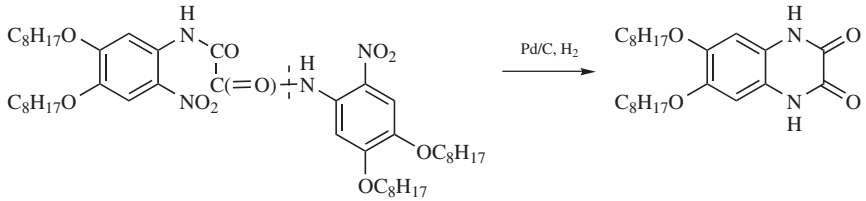
o-{1-Carboxymethyl-2-[*N*-(carboxymethyl)carbamoyl]ethylamino}nitrobenzene (**68**) gave 3-carboxymethyl-3,4-dihydro-2(1*H*)-quinoxalinone (**69**) (Pd/C, H_2, H_2O–EtOH, 20°C: 17%), confirmed in structure by oxidative decarboxylation

during sublimation at 180°C to afford 3-methyl-2(1*H*)-quinoxalinone in 50% yield.[81]



(**68**) (**69**)

N,*N*′-Bis(2-nitro-4,5-dioctyloxyphenyl)oxamide (**70**) gave 6,7-dioctyloxy-2,3(1*H*,4*H*)-quinoxalinedione (**71**) [Pd/C, H_2 (''medium pressure''), $CHCl_3$–MeOH, 20°C, 12 h: 27%).[27]



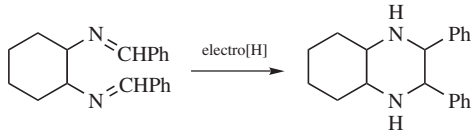
(**70**) (**71**)

Also other examples.[739]

1.1.3. By Formation of the C2,C3 Bond

The only recent (as of 2003) use of such bond formation involves two carbon atoms that are activated by double bonds or as isocyanides. The following examples illustrate the present limited scope of this type of synthesis.

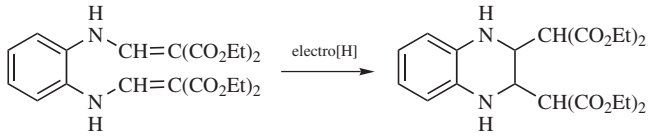
1,2-Bis(benzylideneamino)cyclohexane (**72**) gave 2,3-diphenyldecahydroquinoxaline (**73**) (Pb cathode, C anode, Et_4NOTs, MsOH, Me_2NCHO: 59%); analogs likewise.[118]



(**72**) (**73**)

o-Bis[(2,2-diethoxycarbonylvinyl)amino]benzene (**74**) gave 2,3-bis(diethoxycarbonylmethyl)-1,2,3,4-tetrahydroquinoxaline (**75**) (Hg cathode, Pt anode,

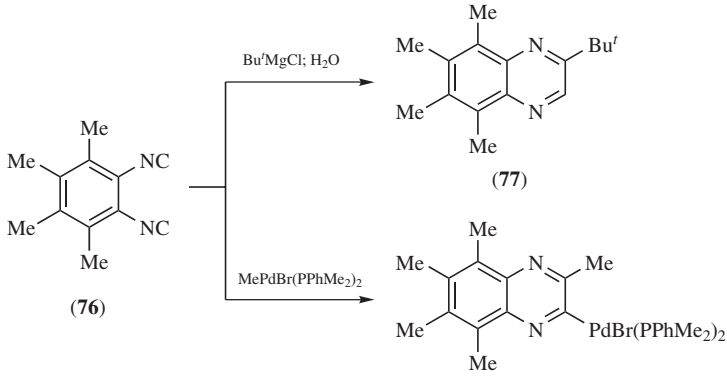
Et_4NClO_4, MeCN–H_2O: 92%); analogs likewise.[127,905]



(**74**) (**75**)

1,2-Diisocyano-5,6,7,8-tetramethylbenzene (**76**) gave a separable mixture of 2-*tert*-butyl-5,6,7,8-tetramethylquinoxaline (**77**) and several oligomers (Bu^tMgCl, THF, 0°C; then $H_2O\downarrow$: 12% isolated yield of monomer; for mechanism, see original).[102]

In contrast, the same substrate (**76**) gave only the monomeric palladium complex (**78**), characterized by X-ray analysis and spectra [$MePdBr(OPPhMe_2)_2$, THF, 20°C: >95%].[999]



(**76**) (**77**) (**78**)

1.2. FROM A BENZENE SUBSTRATE WITH AN ANCILLARY SYNTHON

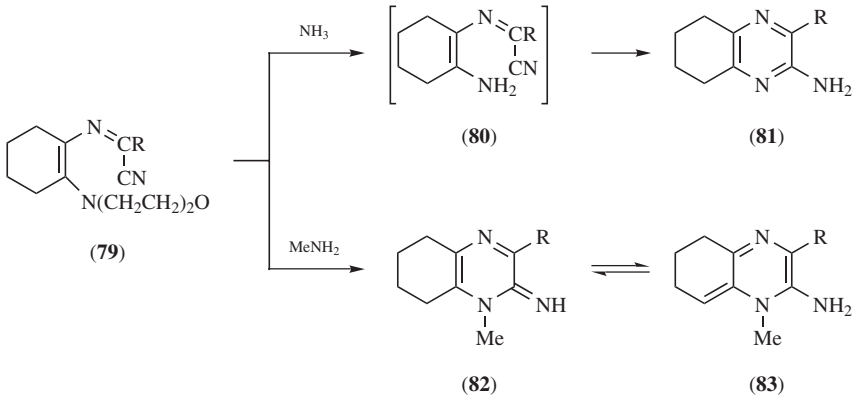
Most published primary syntheses of quinoxalines fall into this category, which is subdivided according to the ring atom(s) supplied by the synthon. The rare cases, in which the synthon is a heterocyclic compound, are covered in Sections 1.5–1.7.

1.2.1. When the Synthon Supplies N1 of the Quinoxaline

Although rarely used, this synthesis is represented by two distinct procedures illustrated in the following examples.

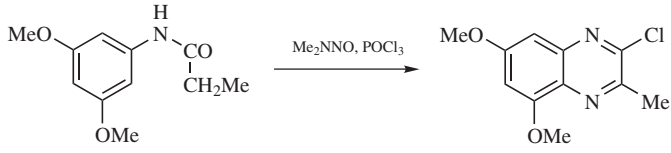
1-(Dicyanomethyleneamino)-2-morpholinocyclohexene (**79**, R = CN) gave 3-amino-5,6,7,8-tetrahydro-2-quinoxalinecarbonitrile (**81**, R = CN), presumably by initial transamination and subsequent cyclization of the intermediate (**80**) (NH_3, MeOH–CH_2Cl_2, 20°C: 84%);[54] also, 1-(α-cyano-α-methoxycarbonylmethyleneamino)-2-morpholinocyclohexene (**79**, R = CO_2Me) gave methyl 3-amino-5,6,7,8-tetrahydro-2-quinoxalinecarboxylate (**81**, R = CO_2Me) (likewise: 49%).[54]

The substrates (**79**, R = CN or CO_2Me) also gave 3-imino-4-methyl-3,4,5,6,7,8-hexahydro-2-quinoxalinecarbonitrile (**82**, R = CN) or methyl 3-imino-4-methyl-3,4,5,6,7,8-hexahydro-2-quinoxalinecarboxylate (**82**, R = CO_2Me), rspectively, that appear to exist largely as such in solution but as the amino tautomers (**83**) in the solid state ($MeNH_2$, MeOH—$CHCl_3$, 20°C, 12 h: 69% or 84%, respectively).[50,665] (See also Section 1.1.2.1.)



(**79**) (**80**) (**81**) (**82**) (**83**)

1,3-Dimethoxy-5-propionamidobenzene (**84**) gave 2-chloro-5,7-dimethoxy-3-methylquinoxaline (**85**) (Me_2NNO, $POCl_3$, 0°C→56°C, 90 min: 11%);[524] analogs were made similarly but in even lower yields, probably because of the formation of isomers when unsymmetric substrates were used.

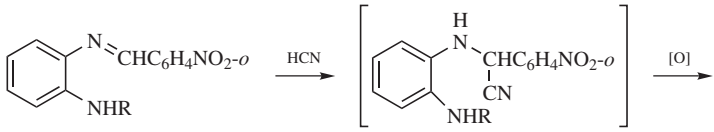


(**84**) (**85**)

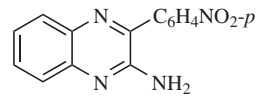
1.2.2. When the Synthon Supplies C2 of the Quinoxaline

Surprisingly little use has been made of this type of synthesis, but it is represented in the following examples.

o-Amino-*N*-(*o*-nitrobenzylidene)aniline (**86**, R = H) gave 3-*o*-nitrophenyl-2-quinoxalinamine (**88**), probably by addition to HCN to give the intermediate (**87**) with subsequent cyclization and aerial aromatization (KCN, H_2O–Me_2NCHO, 20°C, 3 h: 60%);[537] similar treatment of the acetamido substrate (**86**, R = Ac) gave the same product (**88**) (72%).[537]

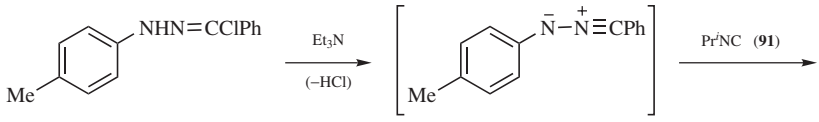


(**86**) (**87**)

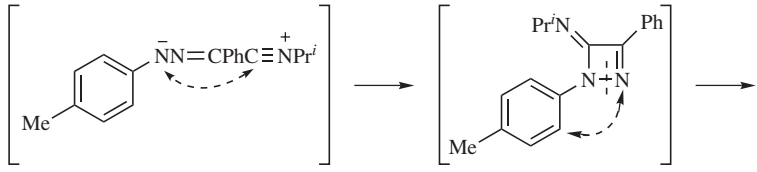


(**88**)

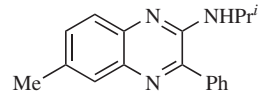
p-[(α-Chlorobenzylidene)hydrazino]toluene (**89**), converted into the zwitterion (**90**), reacted with isopropyl isocyanate (**91**) to give (among other separable products) 2-isopropylamino-6-methyl-3-phenylquinoxaline (**94**), probably via the intermediates (**92** and **93**) (Et_3N, PhH, reflux, 1 h: 5%); several analogs were made similarly but in even lower yield, making this an interesting but impractical synthetic procedure.[207] However, later modifications did produce 2-(ethoxycarbonylmethyl)amino-6-methoxy-3-phenylquinoxaline in 18% yield.[1084]



(**89**) (**90**)



(**92**) (**93**)



(**94**)

1.2.3. When the Synthon Supplies C2 + C3 of the Quinoxaline
(*H* 203; *E* 79, 94, 205)

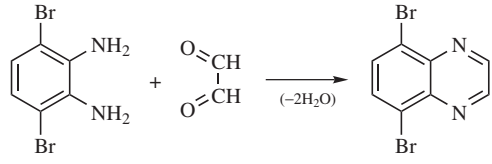
This is by far the most used type of primary synthesis for quinoxalines. It usually involves the cyclocondensation of an *o*-phenylenediamine (or closely related substrate) with a synthon containing an oxalyl [–C(=O)–C(=O)–] or equivalent [e.g., HC(=O)–C≡N] grouping. For convenience, discussion of this synthesis is subdivided according to the type of synthon used to produce formally aromatic quinoxalines; the formation of similar ring-reduced quinoxalines (mostly from related synthons at a lower oxidation state) is included in each such category.

1.2.3.1. Using a Dialdehyde (Glyoxal) or Related Synthon

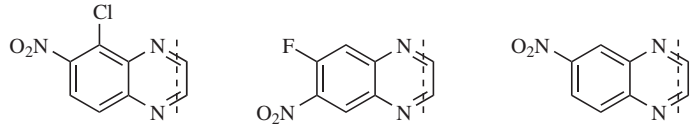
Commercial 40% aqueous glyoxal or the glyoxal–sodium bisulfite adduct may be used satisfactorily with *o*-phenylenediamines to afford 2,3-unsubstituted quinoxalines; the use of an irregular synthon or substrate is also illustrated in the following examples.

With Free Glyoxal as Synthon

3,6-Dibromo-1,2-benzenediamine (**95**) and glyoxal (**96**) gave 5,8-dibromoquinoxaline (**97**) (H_2O–EtOH, reflux, 3 h: 71%);[108] appropriate substrates also gave 5-chloro-6-nitro- (**98**) (likewise, 1 h: 96%),[147] 6-fluro-7-nitro- (**99**) (likewise, 1 h: 81%),[368] and 6-nitroquinoxaline (**100**) (MeCN–H_2O, 50°C, 12 h: 62%).[501]



(**95**) (**96**) (**97**)



(**98**) (**99**) (**100**)

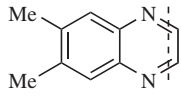
Also other examples.[172,470,533,918,949,970,975]

With Glyoxal–Sodium Bisulfite Adduct as Synthon

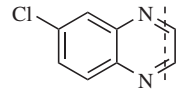
4,5-Dimethyl-1,2-benzenediamine gave 6,7-dimethylquinoxaline (**101**) (OHCCHO·2NaHSO$_3$, H$_2$O, 70°C, 1 h: 78%;[561] OHCCHO, NaHSO$_3$, H$_2$O, 70°C→20°C: 76%;[1043] likewise, 60°C, 45 min: 71%).[160]

4-Chloro-1,2-benzenediamine gave 6-chloroquinoxaline (**102**) (OHCCHO·2NaHSO$_3$·H$_2$O, AcONA, AcOH–H$_2$O, 50°C→60°C, 2 h: 79%;[263] OHCCHO·2NaHSO$_3$·H$_2$O, H$_2$O, 70°C, 1 h: 79%).[561]

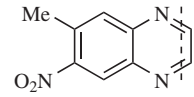
4-Methyl-5-nitro-1,2-benzenediamine gave 6-methyl-7-nitroquinoxaline (**103**) (OHCCHO·2NaHSO$_3$·H$_2$O, H$_2$O, 70°C, ? min: 94%).[936]



(**101**)



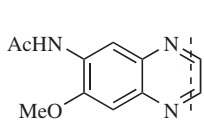
(**102**)



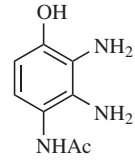
(**103**)

4-Acetamido-5-methoxy-1,2-benzenediamine (prepared in situ by reduction of 1-acetamido-2-methoxy-4,5-dinotrobenzene) gave 6-acetamido-7-methoxyquinoxaline (**104**) (OHCCHO·2NaHSO$_3$·H$_2$O, 70°C, 2 h: 96%).[282]

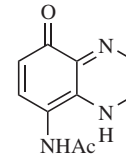
4-Acetamido-2,3-diaminophenol (**105**) (prepared in situ by reduction of the 2,3-dinitro analog) gave 8-acetamido-5(1*H*)-quinoxalinone (**106**) (OHCCHO·2NaHSO$_3$·H$_2$O, reflux, N$_2$↓, 2 h: 79%).[620]



(**104**)



(**105**)



(**106**)

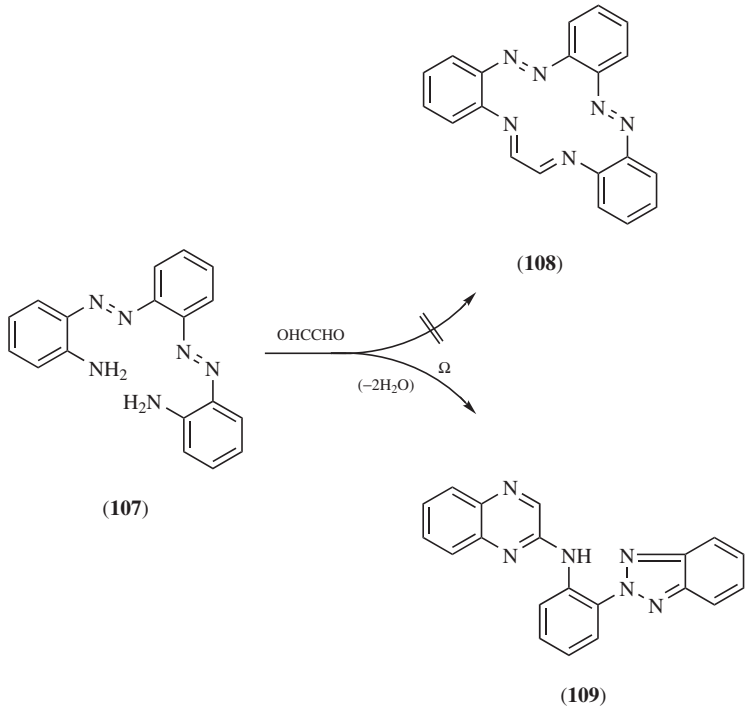
Also other examples in the references cited above and elsewhere.[161,205,247,267,715,750]

With an Irregular Synthon or Substrate

1,2-Diaminocyclohexane and glycol gave decahydroquinoxaline [Ru$_2$(CO)$_{12}$, PBu$_3$, THF, 220°C, A, sealed, 15 h: 88%].[927]

o-Bis(*o*-aminophenylazo)benzene (**107**) and aqueous glyoxal gave, not the expected macrocyclic product (**108**), but 6-[*o*-(benzotriazol-2-yl)anilino]quinoxaline (**109**) (MeOH–H$_2$O, <5°C, 23 h: 59%);[1006] the structure was

confirmed by X-ray analysis and an unambiguous synthesis;[74] and a possible mechanism for the rearrangement has been discussed.[1006]



(**108**)

(**107**)

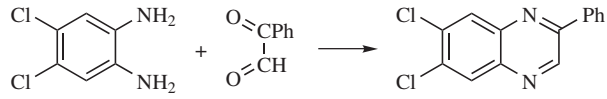
(**109**)

1.2.3.2. Using an Aldehydo Ketone or Related Synthon

Unlike the dialdehyde (glyoxal), aldehydo ketones are essentially unsymmetric; accordingly, they will still give a single product on cyclocondensation with a symmetric *o*-phenylenediamine derivative as substrate, but two isomeric products with an unsymmetric *o*-phenylene derivative. Such isomers are usually separable but often with considerable loss. Mainly to avoid this situation by achieving regioselectivity in syntheses, a variety of aldehydo ketone equivalents have been employed as synthons but with mixed results. The following classified examples illustrate the generalities mentioned above.

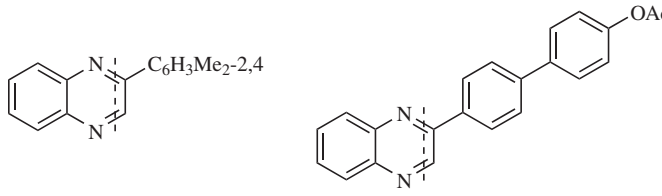
Aldehydo ketones with Symmetric Substrates

4,5-Dichloro-1,2-benzenediamine (**110**) and phenylglyoxal (**111**) gave 6,7-dichloro-2-phenylquinoxaline (**112**) (MeOH, 55°C, 30 min: 73%).[551]



(**110**) (**111**) (**112**)

1,2-Benzenediamine gave 2-(2,4-dimethylphenyl)quinoxaline (**113**) [2,4-$Me_2C_6H_3C(=O)CHO$, AcOH, 100°C, 30 min: 55%][826] or 2-(4′-acetoxybiphenyl-4-yl)quinoxaline (**114**) (*p*-$AcOC_6H_4C_6H_4COCHO$-*p*, EtOH, reflux, ? min: ~70%).[626]

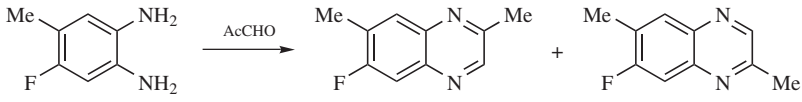


(**113**) (**114**)

Also other examples.[142,186,214,265,333,340,343,526,563,593,728,874]

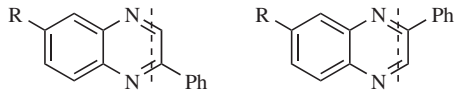
Aldehydo Ketones with Unsymmetric Substrates

4-Fluoro-5-methyl-1,2-benzenediamine (**115**) gave an apparently inseparable mixture of 6-fluoro-2,7-dimethyl-(**116**) and 6-fluoro-3,7-dimethylquinoxaline (**117**) (AcCHO, H_2O, reflux, 15 min: 75%).[6]



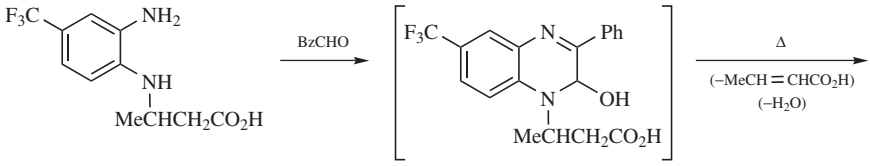
(**115**) (**116**) (**117**)

4-Acetyl-1,2-benzenediamine gave an easily separable mixture of 6-acetyl-2-phenyl- (**118**, R = Ac) and 6-acetyl-3-phenylquinoxaline (**119**, R = Ac) (BzCHO, EtOH, reflux, 3 h: 61% and 18%, respectively);[885] similarly, 4-trifluoromethyl-1,2-benzenediamine gave 2-phenyl-6-trifluoromethyl- (**118**, $R = CF_3$) and 2-phenyl-7-trifluoromethylquinoxaline (**119**, $R = CF_3$) (likewise: 45% and 39%, respectively).[840]

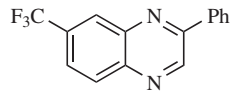


(**118**) (**119**)

2-[(2-Carboxy-1-methylethyl)amino]-5-trifluoromethylaniline (**120**) gave 2-phenyl-7-trifluoromethylquinoxaline (**122**), probably by loss of crotonic acid and water from the unisolated intermediate (**121**) (neat BzCHO, 155°C, 3 h: 82%; note that no isomer was detected).[841]



(**120**) (**121**)

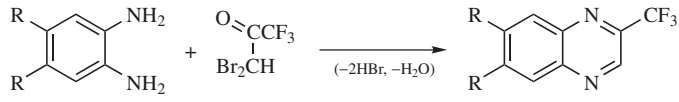


(**122**)

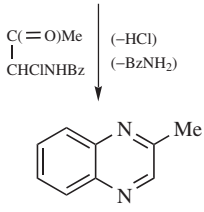
Also other examples affording isomeric pairs that are easy, difficult, or impossible to separate.[5,7,9,25,35,37,296,374,389,756,769,839,843,849]

Aldehydo Ketone Equivalents as Synthons

4,5-Dichloro-1,2-benzenediamine (**123**, R = Cl) and 1,1-dibromo-3,3,3-trifluoroacetone (**124**) gave 6,7-dichloro-2-trifluoromethylquinoxaline (**125**, R = Cl) (MeONa, H_2O, 98°C, 30 min: 83%);[129] 6,7-dimethyl-2-trifluoromethylquinoxaline (**125**, R = Me) was made similarly (57%).[129]



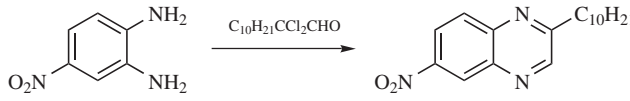
(**123**) (**124**) (**125**)



(**126**)

1,2-Benzenediamine (**123**, R = H) and 1-benzamido-1-chloroacetone gave 2-methylquinoxaline (**126**) (Na_2CO_3, H_2O–EtOH, reflux, 6 h: 70%); homologs likewise.[350]

4-Nitro-1,2-benzenediamine (**127**) gave mainly 2-decyl-6-nitroquinoxaline (**128**) ($C_{10}H_{21}CCl_2CHO \cdot H_2O$-dioxane, pH 9, by $Na_2CO_3\downarrow$, reflux, 2 h: 34% after separation from a little of the 7-nitro isomer).[123]



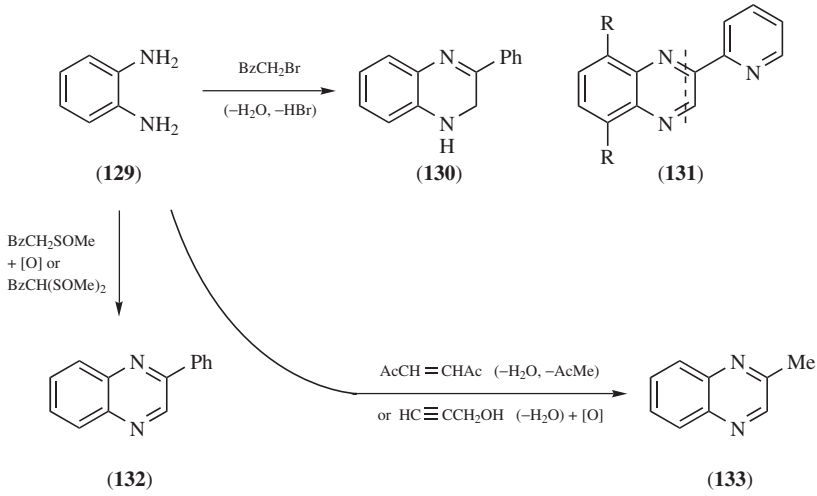
(**127**) (**128**)

Also other examples,[36,258,667,758]

Reduced Analogs of Aldehydo Ketones as Synthons

Note: These synthons will usually give hydroquinoxalines, but some such products may undergo aerial aromatization during the reaction or workup.

1,2-Benzenediamine (**129**) gave 2-phenyl-3,4-dihydroquinoxaline (**130**) (AcONa, MeOH, reflux, $CH_4\downarrow$, 2 h: 55%;[783] with unsymmetric analogs of substrate (**129**), two isomers resulted in each case;[783] and the kinetics of such cyclizations have been studied.[821]



(**129**) (**130**) (**131**)

(**132**) (**133**)

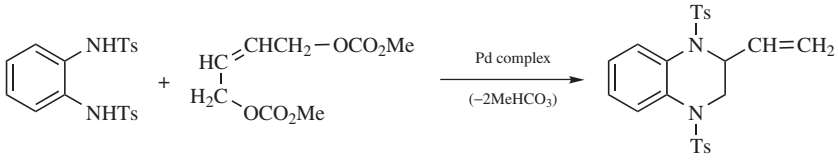
3,6-Diiodo-1,2-benzenediamine gave 5,8-diiodo-2-(pyridin-2-yl)quinoxaline (**131**, R = I) [2-(bromoacetyl)pyridine · HBr, Me_2SO, 60°C, 1 h: 20%; aerial or solvent oxidation?];[172] perhaps by a comparable mechanism, 1,2-benzenediamine

gave 2-(pyridin-2-yl)quinoxaline (**131**, R = H) (2-acetylpyridine, $ClCO_2Me$, PrOH, 50°C, 48 h: 60%).[888]

1,2-Benzenediamine (**129**) gave 2-phenylquinoxaline (**132**) [$BzCH_2SOMe$ or $BzCH(SOMe)_2$, PhH, AcOH, reflux, 2 h: 35% after separation from another product; aerial or sulfoxide oxidation required with the first reagent).[249,cf. 567]

1,2-Benzenediamine (**129**) gave 2-methylquinoxaline (**133**) [AcCH=CHAc (0.5 equiv), CH_2Cl_2, 20°C, 3 days: 80%, with loss of water and acetone;[492] $HC{\equiv}CCH_2OH$, $Hg(OAc)_2$, THF, 20°C, 14 h: 51%].[575]

1,2-Bis(tosylamino)benzene (**134**) and 1,4-bis(methoxycarbonyloxy)but-2-ene (**135**) gave 1,4-ditosyl-2-vinyl-1,2,3,4-tetrahydroquinoxaline (**136**) [Pd complex (made in situ: see original), THF, 25°C, 24 h: 51%]; analogs likewise.[892]



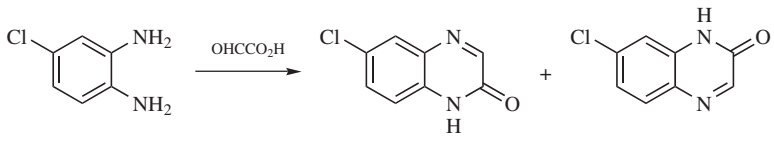
(**134**) (**135**) (**136**)

Also other examples.[402,411,504,1091,1100]

1.2.3.3. Using an Aldehydo Acid or Related Synthon

Such synthons with *o*-phenylenediamines afford 2(1*H*)-quinoxalinones; a single product or two isomers will be formed according to the symmetry of the substrate. Related synthons at a lower oxidation state produce dihydroquinoxalinones. The following examples illustrate typical results.

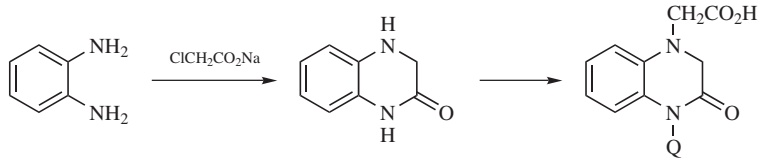
4-Chloro-1,2-benzenediamine (**137**) and glyoxylic acid gave a mixture of 6-chloro- (**138**) and 7-chloro-2(1*H*)-quinoxalinone (**139**) from which only 6-isomer could be isolated in a pure state ($OHCCO_2H$, H_2O–MeOH, 20°C, 24 h: 37%).[947,1042]



(**137**) (**138**) (**139**)

1,2-Benzenediamino (**140**) and chloroacetic acid (1 equiv) gave 3,4-dihydro-2(1*H*)-quinoxalinone (**141**) ($ClCH_2CO_2Na$, H_2O, reflux, 5 h: ?%);[316,447] an excess of synthon gave 4-carboxymethyl- (**142**, Q = H) and/or 1,4-bis-

(carboxymethyl)-3,4-dihydro-2(1*H*)-quinoxalinone (**142**, $Q = CH_2CO_2H$) (similar conditions: ?%).[261,425]



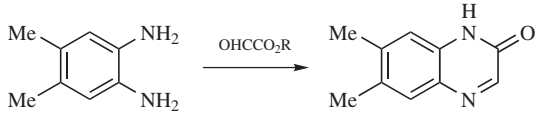
(**140**) (**141**) (**142**)

Also other examples.[382,708,1062]

1.2.3.4. Using an Aldehydo Ester or Related Synthon

These synthons behave much as do the foregoing aldehydo acids but they are usually more convenient and reactive, as indicated by the following examples.

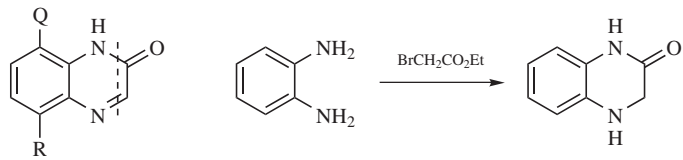
4,5-Dimethyl-1,2-benzenediamine (**143**) gave 6,7-dimethyl-2(1*H*)-quinoxalinone (**144**) [$OHCCO_2Me$, EtOH, reflux, 2 h: 72%;[718] or $OHCCO_2Bu$, similarly: 69%].[697]



(**143**) (**144**)

3-Fluoro-1,2-benzenediamine gave a separable mixture of 5-fluoro- (**145**, Q = H, R = F) and 8-fluoro-2(1*H*)-quinoxalinone (**145**, Q = F, R = H) ($OHCCO_2Bu$, H_2O–EtOH, reflux, $N_2\downarrow$, 3 h: 16% and 23%, respectively, after separation).[708]

1,2-Benzenediamine (**146**) gave 3,4-dihydro-2(1*H*)-quinoxalinone (**147**) (BrH_2CCO_2Et, Et_3N, CH_2Cl_2-THF, 20°C, 14 h; then 60°C, 3 h: 62%).[425,447,821]



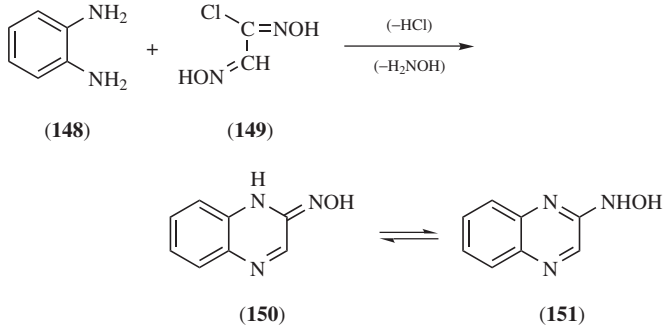
(**145**) (**146**) (**147**)

Also other examples.[22,648]

1.2.3.5. Using an Aldehydo Amide, Nitrile, Acyl Halide, or Related Synthon

Each such category of synthon has potential for the synthesis of quinoxalines or hydroquinoxalines, but very few examples have been reported.

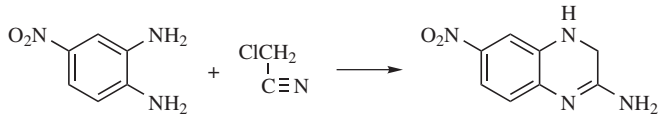
1,2-Benzenediamine (**148**) and *trans*-1-chloro-1,2-bis(hydroxyimino)ethane (**149**) gave 2(1*H*)-quinoxalinone oxime (**150**), perhaps better formulated as 2-hydroxyaminoquinoxaline (**151**) (EtOH, 20°C, 3 h: 71%);[992,cf. 982] 6,7-dibromo-1,2-benzenediamine likewise gave 6,7-dibromo-2-hydroxyaminoquinoxaline.[850]



(**148**) (**149**) (**150**) (**151**)

4-Nitro-1,2-benzenediamine (**152**) and chloroacetonitrile (**153**) gave 6-nitro-3,4-dihydro-2-quinoxalinamine (**154**), apparently without 7-nitro isomer (Et_3N, *p*-xylene, reflux, 6 h: 47%).[53]

Also other examples.[562,850]



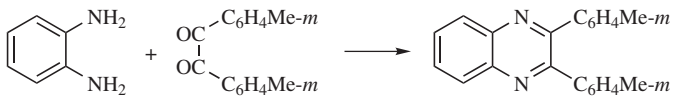
(**152**) (**153**) (**154**)

1.2.3.6. Using a Diketone or Related Synthon

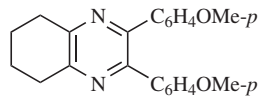
Diketones, like diacetyl and related synthons, react readily with *o*-phenylenediamines or related reduced substrates to afford quinoxalines. Only when both synthon and substrate are unsymmetric are two isomers formed, and this situation has been largely avoided in recent literature. The following classified examples illustrate many of the possibilities available from such syntheses.

Regular Diketones as Synthons: One Product

1,2-Benzenediamine (**155**) and *m*,*m*′-dimethylbenzil (**156**) gave 2,3-di-*m*-tolylquinoxaline (**157**) (EtOH, reflux, 2 h: 93%);[218] similarly, 1,2-diaminocyclohexane and *p*,*p*′-dimethoxybenzil gave 2,3-bis(*p*-methoxyphenyl)-5,6,7,8-tetrahydroquinoxaline (**158**), via oxidation of the unisolated 4a,5,6,7,8,8a-hexahydro analogue (MeOH, reflux, 1 h; then crude product, S, 140°C, ? min: 36%).[600]



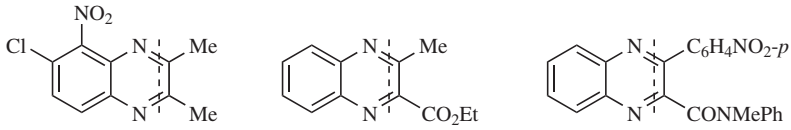
(**155**) (**156**) (**157**)



(**158**)

4-Chloro-3-nitro-1,2-benzenediamine gave 6-chloro-2,3-dimethyl-5-nitroquinoxaline (**159**) (Ac_2, EtOH, 60°C, 20 min: 84%);[470] analogs likewise.[470,828]

1,2-Benzenediamine gave ethyl 3-methyl-2-quinixalinecarboxylate (**160**) [AcC(=O)CO_2Et (made in situ), TsOH, PhH, reflux, 2 h: 74%][119] or *N*-methyl-3-*p*-nitrophenyl-*N*-phenyl-2-quinoxalinecarboxamide (**161**) [BzC(=O)-CONMePh, AcOH, reflux, 30 min: 76%].[582]

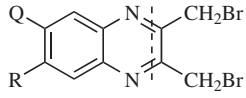


(**159**) (**160**) (**161**)

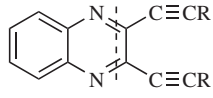
1,2-Benzenediamine gave 2,3-bis(bromomethyl)quinoxaline (**162**, Q = R = H) [$BrH_2CC(=O)C(=O)CH_2Br$, EtOH, 0°C, 30 min: 81%];[297,1043] 4,5-dimethyl-1,2-benzenediamine gave 2,3-bis(bromomethyl)-6,7-dimethylquinoxaline (**162**, Q = R = Me) (similarly: 70%;[185] or PhH, reflux, 40 min: 75%);[951] and 3-nitro-1,2-benzenediamine gave 2,3-bis(bromomethyl)-5-nitroquinoxaline (**162**, $Q = NO_2$, R = H) [$BrH_2CC(=O)C(=O)CH_2Br$, MeOH, O°C, 2 h: 88%].[882]

1,2-Benzenediamine gave 2,3-bis[(triisopropylsilyl)ethynyl]quinoxaline (**163**, $R = SiPr^i_3$) [$Pr^i_3SiC{\equiv}CC(=O)C(=O)C{\equiv}CSiPr^i_3$, "activated molecular sieve," PhMe, 80°C, 20 min: 95%) or 2,3-bis(phenylethynyl)quinoxaline (**163**, R = Ph) [$PhC{\equiv}CC(=O)C(=O)C{\equiv}CPh$, likewise: 80%).[656]

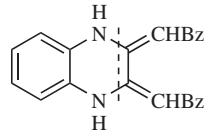
1,2-Benzenediamine gave 2,3-diphenacylquinoxaline, shown by X-ray analysis to exist as its tautomer (**164**) at least in the solid state [$BzCH_2C(=O)C(=O)CH_2Bz$, EtOH, reflux, 30 min: 80%];[1037] 1,2-diaminocyclohexane likewise gave 2,3-diphenacyl-4a,5,6,7,8,8a-hexahydroquinoxaline (70%), also in the diphenacyidene form akin to structure **164**.[1037]



(**162**)



(**163**)

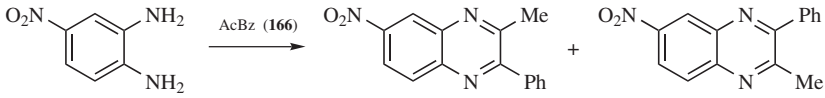


(**164**)

Also many other examples[24,37,61,70,87,96,110,114,126,162,171,172,256,276,289,326,334,339,360,401,444,509,514,529,534,548,566,577,611,638,678,702,816,895,902,955,981,1000,1009] including a good solid-state procedure.[1065]

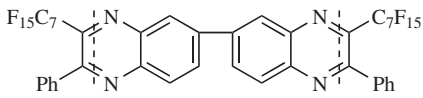
Regular Diketones as Synthons: Two Isomeric Products

4-Nitro-1,2-benzenediamine (**165**) and 1-methyl-2-phenylglyoxal (**166**) gave a mixture of 2-methyl-7-nitro- (**167**) and 2-methyl-6-nitro-3-phenylquinoxaline (**168**) (MeOH, reflux, ? min: >70%), subsequently separated chromatographically with considerable (?) loss;[420] also analogous examples.[420]



(**165**) (**167**) (**168**)

3,3′,4,4′-Biphenyltetramine and 1-(perfluoroheptyl)-2-phenylglyoxal gave a product formulated as 3,3′-bis(perfluoroheptyl)-2,2′-diphenyl-6,6′-biquinoxaline (**169**) (*m*-cresol, 20°C, 24 h: 92%; possibly containing both other possible isomers).[900]



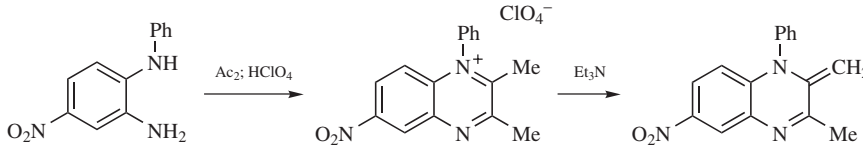
(**169**)

Also other examples.[77]

Regular Diketones as Synthons with *o*-Alkylaminoanilines

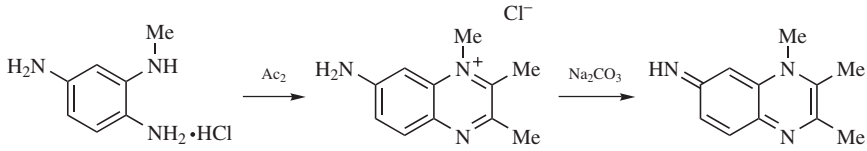
Note: This combination has been used in acidic media to produce quaternized quinoxalines.

2-Anilino-5-nitroaniline (**170**) gave 2,3-dimethyl-6-nitro-1-phenylquinoxalinium perchlorate (**171**) (Ac_2, $HClO_4$, BuOH–Et_2O–H_2O, 20°C, 20 min: 84%) and thence 2-methyl-3-methylene-7-nitro-4-phenyl-3,4-dihydroquinoxaline (**172**) (Et_3N, AcMe, warm: 79%);[63] analogs likewise.[63,67]



(**170**) (**171**) (**172**)

2-Methylamino-1,4-benzenediamine hydrochloride (**173**) gave 7-amino-1,2,3-trimethylquinoxalinium chloride (**174**) (Ac_2, no details) and thence 2,3,4-trimethyl-6(4*H*)-quinoxalinimine (**175**) (Na_2CO_3, no details).[174]

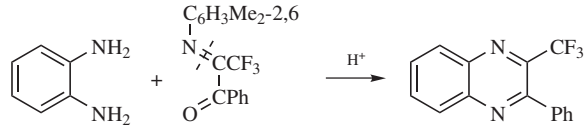


(**173**) (**174**) (**175**)

Also other examples.[170]

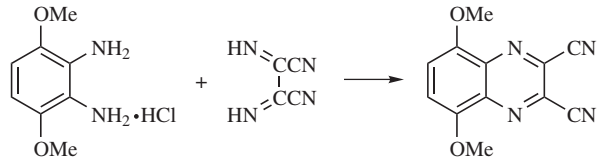
Diketone Equivalents as Synthons

1,2-Benzenediamine (**176**) and *N*-(2-benzoyl-1-trifluoromethylethylidene)-2,6-dimethylaniline (**177**) gave 2-phenyl-3-trifluoromethylquinoxaline (**178**) (HCl, MeOH–H_2O, 20°C, 36 h: >95%).[188]



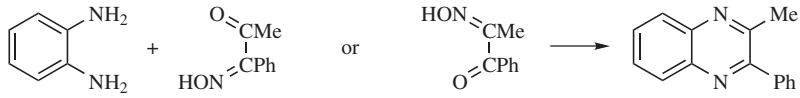
(**176**) (**177**) (**178**)

3,6-Dimethoxy-1,2-benzenediamine hydrochloride (**179**) and diiminosuccinonitrile (**180**) gave 5,8-dimethoxy-2,3-quinoxalinedicarbonitrile (**181**) (F_3CCO_2H, 20°C, 13 h: 77%).[553]



(**179**) (**180**) (**181**)

1,2-Benzenediamine (**182**) and 1-methyl-2-phenylglyoxal 2-oxime (**183a**) or the isomeric 1-oxime (**183b**) gave 2-methyl-3-phenylquinoxaline (**184**) (EtOH, reflux, 90 min: 80% or 90%, respectively);[1033] homologs likewise.[1033]



(**182**) (**183a**) (**183b**) (**184**)

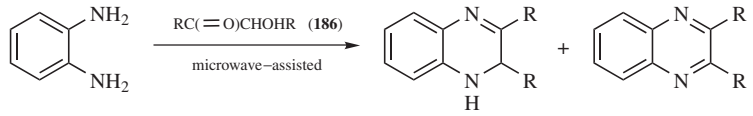
1,2-Benzenediamine and 2-acetyl-2-anilino-2-ethoxy(thioacetanilide) [AcC(OEt)-(NHPh)C(=S)NHPh] gave 3-methyl-2-quinoxalinecarbothioanilide (EtOH, reflux, 3 h: 65%).[1102]

Also other examples.[198,507,662,1117]

Reduced Analogs of Diketones as Synthons

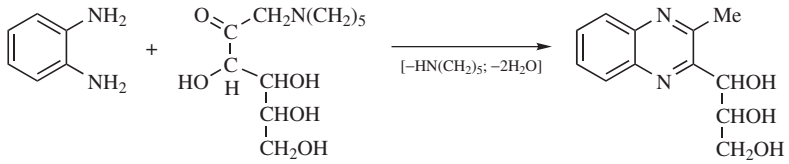
Note: There is considerale variety in this category, including, for example, the use of hydroxyimino- or nitroso derivatives of benzene as substrates.

1,2-Benzenediamine (**185**) and benzoin (**186**) gave a separable mixture of 2,3-diphenyl-1,2-dihydroquinoxaline (**187**, R = Ph) and 2,3-diphenylquinoxaline (**188**, R = Ph) (dry mixture, microwave irradiation under reflux, 4 min: 21% and 67%, respectively); in contrast, similar treatment with *m*,*m*′-dichlorobenzoin gave only the aromatized product, 2,3-bis(*m*-chlorophenyl)quinoxaline (**188**, R = C_6H_4Cl-*m*) (94%).[856]



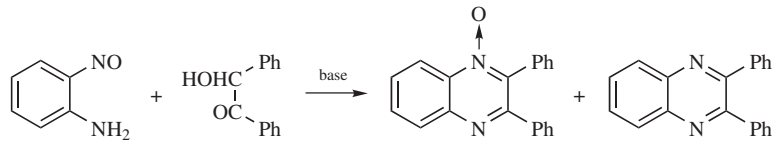
(**185**) (**187**) (**188**)

1,2-Benzenediamine (**189**) and 1-deoxy-1-piperidino-D-fructose (**190**) gave 2-methyl-3-(1,2,3-trihydroxypropyl)quinoxaline (**191**) [phosphate buffer (pH 7), reflux, 10 h: 70%; no external [O] needed].[915]



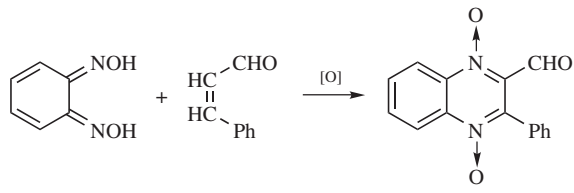
(**189**) (**190**) (**191**)

o-Nitrosoaniline (**192**) and benzoin (**193**) gave a separable mixture of the expected product, 2,3-diphenylquinoxaline 1-oxide (**194**), and some 2,3-diphenylquinoxaline (**195**) (minimal details);[352] also somewhat similar condensations.[345,352]



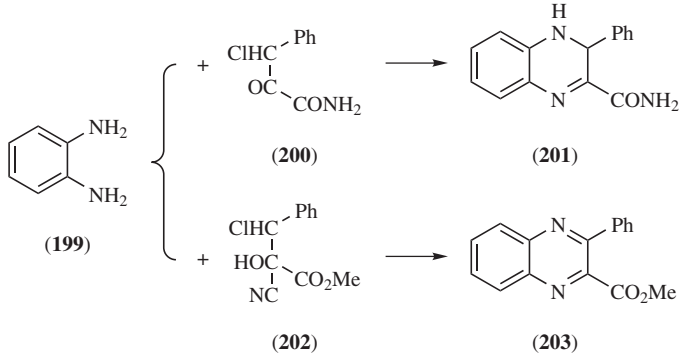
(**192**) (**193**) (**194**) (**195**)

o-Benzoquinone dioxime (**196**) and cinnamaldehyde (**197**) gave 3-phenyl-2-quinoxalinecarbaldehyde 1,4-dioxide (**198**) (MeOH, <20°C, ? h: >35%; clearly involving aerial oxidation).[408]



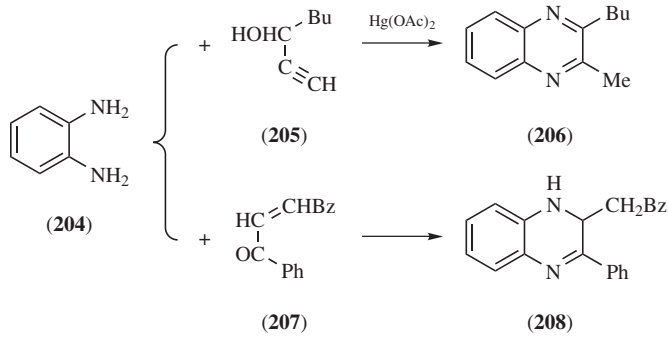
(**196**) (**197**) (**198**)

1,2-Benzenediamine (**199**) and *C*-(2-chloro-2-phenylacetyl)formamide (**200**) gave 3-phenyl-3,4-dihydro-2-quinoxalinecarboxamide (**201**), formulated as its 1,4-dihydro tautomer (EtOH, reflux, 6 h: 56%);[356] in contrast, the same substrate (**199**) with methyl *C*-(2-chloro-2-phenylacetyl)formate cyanohydrin (**202**) gave methyl 3-phenyl-2-quinoxalinecarboxylate (**203**), presumably by aerial oxidation of a dihydro precursor (MeCN, reflux, 12 h: 7%).[859]



(**199**) (**200**) (**201**) (**202**) (**203**)

1,2-Benzenediamine (**204**) and hept-1-yn-3-ol (**205**) gave 2-butyl-3-methylquinoxaline (**206**) [$Hg(OAc)_2$ (oxidant), THF, 60°C→20°C, 15 h: 60%].[575] The same substrate (**204**) and 1,2-dibenzoylethylene (**207**) gave 2-phenacyl-3-phenyl-1,2-dihydroquinoxaline (**208**) (MeOH, reflux, 15 min: 61%; PhH, 45°C, 4 h: 57%).[782]



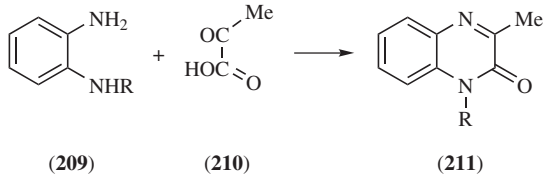
Also other examples.[497,787,1015]

1.2.3.7. Using a Keto Acid or Related Synthon

As they are essentially unsymmetric, such synthons will give a single quinoxalinone only when the *o*-phenylenediamine or related substrate is symmetric or one of its amino groups is secondary. The following examples illustrate conditions and the yields to be expected.

Reactions Giving a Single Unambiguous Product

1,2-Benzenediamine (**209**, R = H) and pyruvic acid (**210**) gave 3-methyl-2(1*H*)-quinoxalinone (**211**, R = H) (HCl–H_2O, 20°C, 15 min: 75%; or H_2O, 20°C, 10 min: 65%).[996] *o*-Methylaminoaniline (**209**, R = Me) and the same synthon (**210**) gave 1,3-dimethyl-2(1*H*)-quinoxalinone (**211**, R = Me) (EtOH, 50°C, briefly: 77%).[1005]

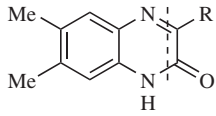


4,5-Dimethyl-1,2-benzenediamine with phenylglyoxylic acid ($PhCOCO_2H$) gave 6,7-dimethyl-3-phenyl-2(1*H*)-quinoxalinone (**212**, R = Ph) (EtOH, reflux,

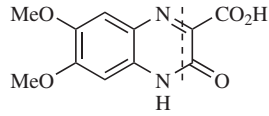
10 min: 72%)[964] or with benzoylpyruvic acid ($BzCH_2COCO_2H$) gave 6,7-dimethyl-3-phenacyl-2(1*H*)-quinoxalinone (**212**, $R = CH_2Bz$) (EtOH, 20°C, 3 h: 93).[222]

4,5-Dimethoxy-1,2-benzenediamine with mesoxalic acid (HO_2CCOCO_2H) gave 6,7-dimethoxy-3-oxo-3,4-dihydro-2-quinoxalinecarboxylic acid (**213**) (0.5M HCl, 98°C, 2 h: 56%).[943]

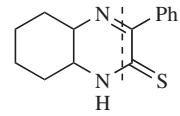
1,2-Cyclohexanediamine with diphenacyl sulfide, appearing to react as benzoyl(thiopyruvic) acid, gave a separable mixture of *cis*- and *trans*-3-phenyl-4a,5,6,7,8,8a-hexahydro-2(1*H*)-quinoxalinethione (**214**) [$HOCH_2CH_2OH$–EtOH, 20°C, 10 days (or reflux, 4 h): 10% and 6%, respectively].[426]



(**212**)



(**213**)

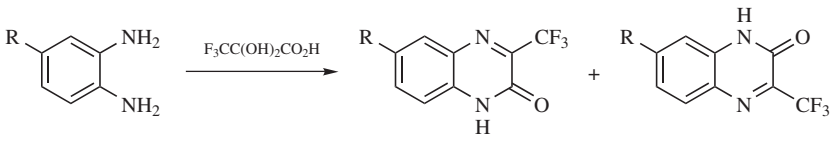


(**214**)

Also other examples.[23,240,372,383,592,690,811,1046,1118]

Reactions Giving Isomeric Products

4-Methyl-1,2-benzenediamine (**215**, R = Me) with the hydrate of 3,3,3-trifluoropyruvic acid gave a mixture of isomers (**216**, R = Me) and (**217**, R = Me) (dioxane, reflux, 30 min: 98%) from which neither appears to have been isolated in a pure state;[165] in contrast, 4-nitro-1,2-benzenediamine (**215**, $R = NO_2$) and the same synthon gave a mixture of 6-nitro- (**216**, $R = NO_2$) and 7-nitro-3-trifluoromethyl-2(1*H*)-quinoxalinone (**217**, $R = NO_2$) (dioxane, reflux, 4 h: 95%), from which both isomers were isolable, albeit with considerable loss.[165]



(**215**) (**216**) (**217**)

Also other examples.[204]

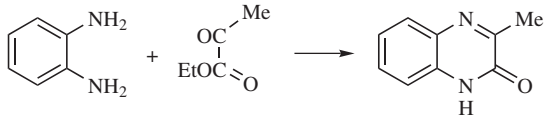
1.2.3.8. Using a Keto Ester or Related Synthon

Like keto acids, the corresponding esters can give a single product or a mixture of isomers according to the symmetry of the reactants. Keto esters and the like have

been used extensively in recent literature, although kinetic studies[458] suggest that they react 100–1000 times more slowly than do the corresponding acids.

Regular Keto Esters as Synthons: One Product

1,2-Benzenediamine (**218**) and ethyl pyruvate (**219**) gave 3-methyl-2(1*H*)-quinoxalinone (**220**) (EtOH, reflux, 3 h: >95%).[84]

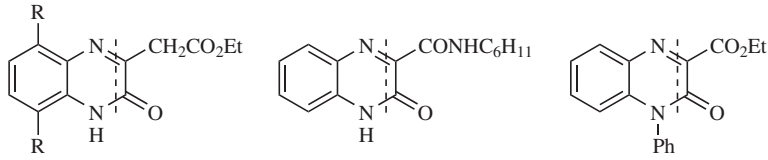


(**218**) (**219**) (**220**)

The same substrate (**218**) and ethyl ethoxalylacetate ($EtO_2CCOCH_2CO_2Et$) gave 3-ethoxycarbonylmethyl-2(1*H*)-quinoxalinone (**221**, R = H) (EtOH, reflux, 3 h: 80%;[505] likewise but 15 min: 64%);[237] the homologous substrate, 3,6-dimetyl-1,2-benzenediamine, and the same synthon gave 3-ethoxycarbonylmethyl-5,8-dimethyl-2(1*H*)-quinoxalinone (**221**, R = Me) (AcOH, reflux, briefly: 61%).[79]

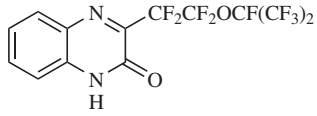
1,2-Benzenediamine (**218**) and the hydrochloride of ethyl 2-[*N*-cyclohexyl-(ethoxyformimidoyl)]glyoxalate [$EtO_2CCOC(OEt)=N(C_6H_{11})$] (prepared in situ) gave *N*-cyclohexyl-3-oxo-3,4-dihydro-2-quinoxalinecarboxamide (**222**) (PhH–EtOH–CH_2Cl, 40°C, 2 h: 81%; clearly needing an hydrolytic step).[698]

o-Anilinoaniline gave ethyl 3-oxo-4-phenyl-3,4-dihydro-2-quinoxalinecarboxylate (**223**) (EtO_2CCOCO_2Et, xylene, reflux, A, 43 h: 82%).[535]



(**221**) (**222**) (**223**)

1,2-Benzenediamine gave 3-perfluoro(2-isopropoxyethyl)-2(1*H*)-quinoxalinone (**224**) [$EtO_2CC(=O)CF_2CF_2OCF(CF_3)_2$, EtOH, reflux, 48 h: 77%].[896]

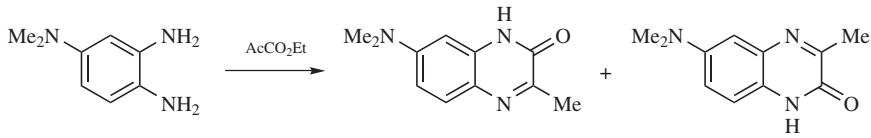


(**224**)

Also other examples.[146,167,209,303,323,356,358,493,544,686,688,689,785,797,822,832,833,846,903,977]

Regular Keto Esters ss Synthons: Two Products

4-Dimethylamino-1,2-benzenediamine (**225**) gave a separable mixture of 7-dimethylamino- (**226**) and 6-dimethylamino-3-methyl-2(1*H*)-quinoxalinone (**227**) ($AcCO_2Et$, EtOH, reflux, N_2, 4 h: 70% and 25%, respectively).[72]



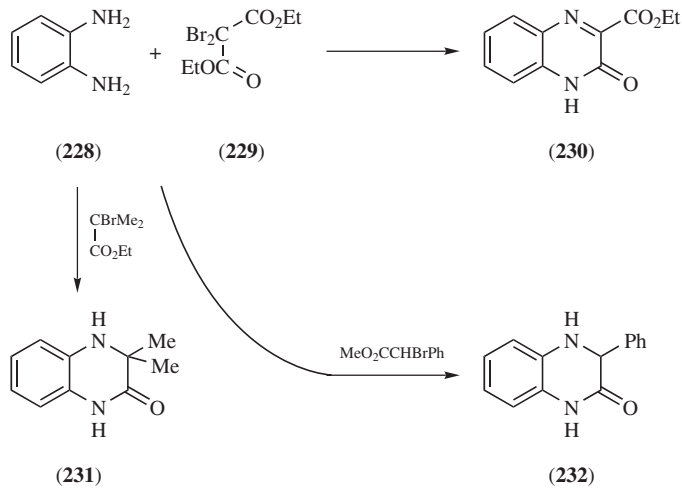
(**225**) (**226**) (**227**)

Also other examples.[458]

Equivalents or Reduced Analogs of Keto Esters as Synthons

1,2-Benzenediamine (**228**) and diethyl dibromomalonate (**229**) gave ethyl 3-oxo-3,4-dihydro-2-quinoxalinecarboxylate (**230**) (MeOH, 20°C, 24 h: 40%).[448]

The same substrate (**228**) with ethyl α-bromoisobutyrate gave 3,3-dimethyl-3,4-dihydro-2(1*H*)-quinoxalinone (**231**) (Me_2NCHO, $NEtPr^i_2$, 110°C, 7 h: 76%);[724] or with methyl 2-bromo-2-phenylacetate gave 3-phenyl-3,4-dihydro-2(1*H*)-quinoxalinone (**232**) (KI, K_2CO_2, AcMe, reflux, 12 h; then oily product, MeONa, PhH, reflux, 7 h: 89%).[159]



(**228**) (**229**) (**230**)

(**231**) (**232**)

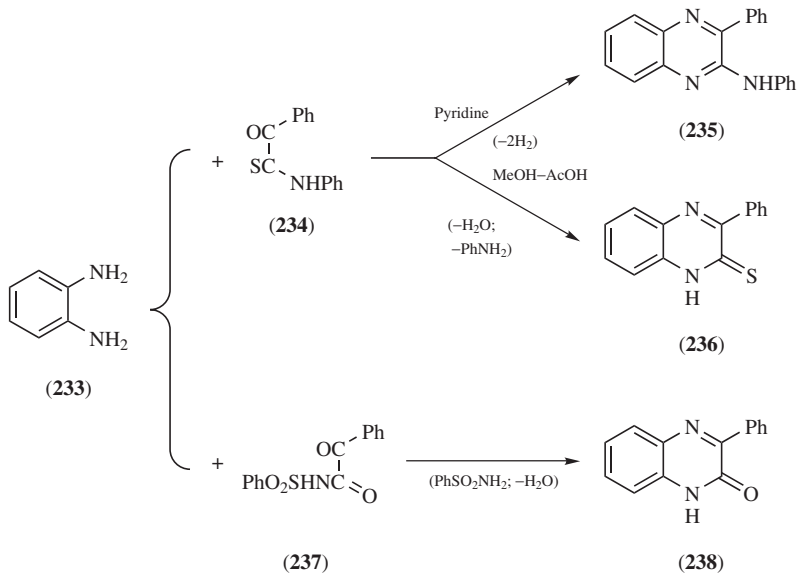
Also other examples.[76,295,307,499,721]

1.2.3.9. Using a Keto Amide, Nitrile, Acyl Halide, or Related Synthon

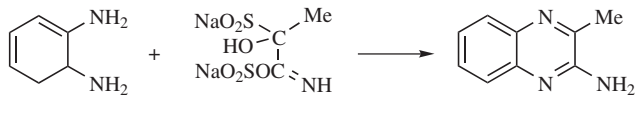
Keto amides (or thioamides) could participate in cyclocondensations by elimination of the amino or oxo (thioxo) function from the amide (thioamide) grouping according to conditions. The other synthons should behave reasonably predictably. The following examples illustrate some possibilities.

1,2-Benzenediamine (**233**) and *C*-benzoyl-*N*-phenyl(thioformamide) (**234**) gave 2-anilino-3-phenylquinoxaline (**235**) (pyridime, reflux, 10 h: 81%) or 3-phenyl-2(1*H*)-quinoxalinethione (**236**) (MeOH–AcOH, 20°C, N_2, 3 days: 46%);[946] several analogs were made similarly.[946]

The same substrate (**233**) and *N*-benzenesulfonyl-*C*-benzoylformamide (**237**) gave only 3-phenyl-2(1*H*)-quinoxalinone (**238**) (MeOH, reflux, 15 min: 57% MeOH–H_2O, reflux, 1 h: 46%; neat reactants, 90°C, 5 min: 41%).[755]

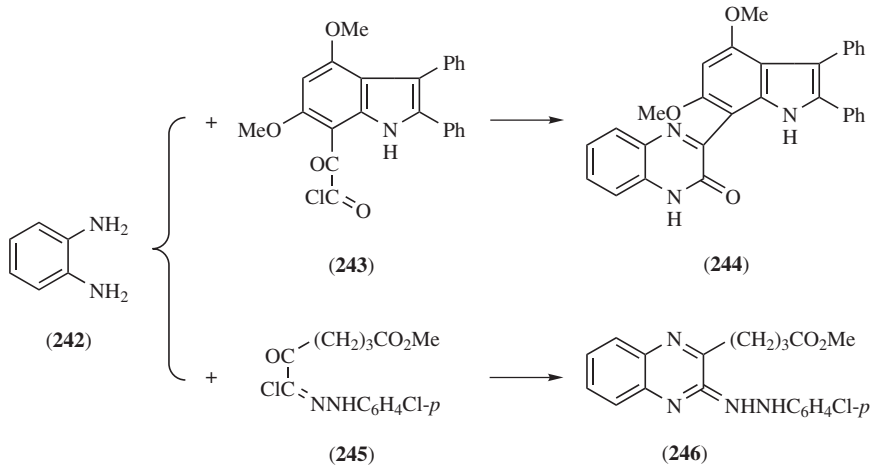


1,2-Benzenediamine (**239**) and the bisbisulfite complex (**240**) (isolated from isonitrosoacetone and an excess of aqueous $NaHSO_3$) gave 3-methyl-2-quinoxalinamine (**241**) (no details: 70%).[758]



1,2-Benzenediamine (**242**) and 7-chloroxalyl-4,6-dimethoxy-2,3-diphenylindole (**243**) gave 3-(4,6-dimethoxy-2,3-diphenylindol-7-yl)-2(1*H*)-quinoxalinone (**244**) (pyridine–CH_2Cl_2, reflux, 90 min: 40%).[652]

The same substrate (**242**) and methyl 4-[2-chloro-2-(*p*-chlorophenylhydrazono) acetyl]butyrate (**245**) gave 2-(*p*-chlorophenylhydrazino)-3-(3-methoxycarbonylpropyl)quinoxaline (**246**) (Et_3N, EtOH, reflux, 15 min: 42%).[878]



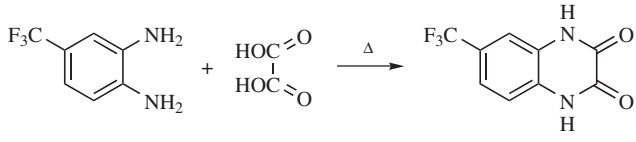
Also other examples.[154,347,364,823]

1.2.3.10. Using a Diacid (Oxalic Acid) as Synthon

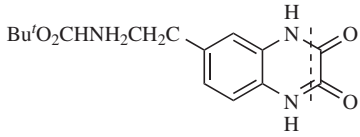
No variation in synthon is possible in this category, but the substrate can bear a variety of substituents to afford substituted 2,3(1*H*,4*H*)-quinoxalinediones. The following examples are classified according to the general procedures used.

By Heating Neat Substrate and Oxalic Acid

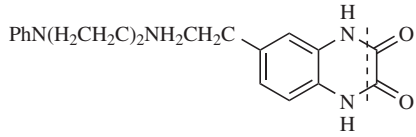
4-Trifluoromethyl-1,2-benzenediamine (**247**) and oxalic acid (**248**) (as dihydrate) gave 6-trifluoromethyl-2,3(1*H*,4*H*)-quinoxalinedione (**249**) (neat reactants, 130°C, 3 h: 87%).[478]



4-[2-(*tert*-Butoxycarbonylamino)ethyl]-1,2-benzenediamine gave 6-[2-(*tert*-butoxycarbonylamino)ethyl]-2,3(1*H*,4*H*)-quinoxalinedione (**250**) [neat $(CO_2H)_2 \cdot 2H_2O$, 185°C, A, 3 h: 67%].[871]



(**250**)



(**251**)

4-[2-(4-phenylpiperazin-1-yl)ethyl]-1,2-benzenediamine gave 6-[2-(4-phenylpiperazin-1-yl)ethyl]-2,3(1*H*,4*H*)-quinoxalinedione (**251**) [neat $(CO_2H)_2$, 200°C, N_2, 30 min: ?%].[872]

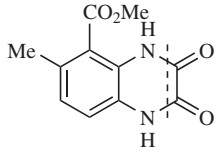
Also other examples.[321]

By Reaction in Dilute Hydrochloric Acid

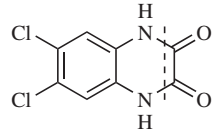
Methyl 2,3-diamino-6-methylbenzoate gave methyl 6-methyl-2,3-dioxo-1,2,3,4-tetrahydro-5-quinoxalinecarboxylate (**252**) [$(CO_2H)_2$, 4M HCl, reflux, 90 min: 69%; note survival of the ester grouping].[506]

2,3-Diamino-5,6-dichlorotoluene gave 6,7-dichloro-5-methyl-2,3(1*H*,4*H*)-quinoxalinedione (**253**) [$(CO_2H)_2$, 4M HCl, reflux, 6 h: 66%],[1039]

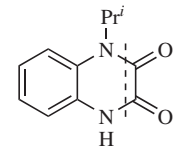
2-Isopropylaminoaniline gave 1-isopropyl-2,3(1*H*,4*H*)-quinoxalinedione (**254**) [$(CO_2H)_2$, 6M HCl, 100°C, 1 h: 94%].[950]



(**252**)



(**253**)



(**254**)

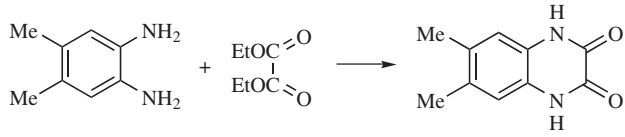
Also other examples.[14,48,279,681,694,697,723,1003,1045]

1.2.3.11. Using a Diester (a Dialkyl Oxalate) or Related Synthon

Like oxalic acid, oxalic esters and *o*-phenyldiamines give 2,3(1*H*,4*H*)-quinoxalinediones that bear substituents according to those on the substrate; such condensations appear to be assisted substantially by microwave irradiation.[1036] The corresponding half-imidic esters have also been used to afford 3-amino-2(1*H*)-quinoxalinones. The following examples illustrate typical conditions and yields.

Regular Diesters as Synthons

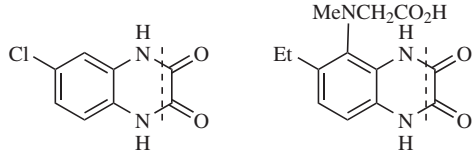
4,5-Dimethyl-1,2-benzenediamines (**255**) and diethyl oxalate (**256**) gave 6,7-dimethyl-2,3(1*H*,4*H*)-quinoxalinedione (**257**) (THF, trace AcOH, reflux, A, 3 days: 96%).[46]



(**255**) (**256**) (**257**)

4-Chloro-1,2-benzenediamine gave 6-chloro-2,3(1*H*,4*H*)-quinoxalinedione (**258**) [neat $(CO_2Et)_2$, reflux, 16 h: 98%]; also some analogs.[716]

3-(*N*-Carboxymethyl-*N*-methylamino)-4-ethyl-1,2-benzenediamine gave 5-(*N*-carboxymethyl-*N*-methylamino)-6-ethyl-2,3(1*H*,4*H*)-quinoxalinedione (**259**) [$(CO_2Me)_2$, EtOH, reflux, 16 h: 45%].[1003]



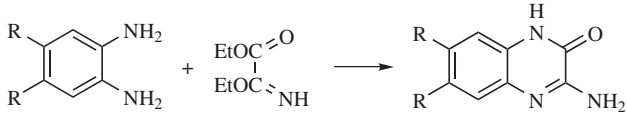
(**258**) (**259**)

Also other examples.[243,687,805,812,814,1036]

Synthons Related to Diesters

Note: When such synthons are unsymmetric, they can give rise to isomeric products on condensation with unsymmetric substrates.

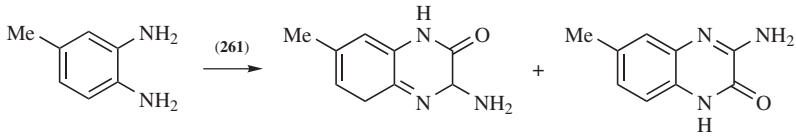
1,2-Benzenediamine (**260**, R = H) and ethyl (*C*-ethoxyformimidoyl)formate (**261**) gave 3-amino-2(1*H*)-quinoxalinone (**262**, R = H) (EtOH, reflux, 1 h: >95%;[580] EtOH, 25°C, >8 h: 82%).[562]



(**260**) (**261**) (**262**)

4,5-Dichloro-1,2-benzenediamine (**260**, R = Cl) likewise gave 3-amino-6,7-dichloro-2(1*H*)-quinoxalinone (**262**, R = Cl) (EtOH, reflux, 1 h: 58%;[580] EtOH, 25°C, >8 h: 78%);[562] also analogs.[562,580,670]

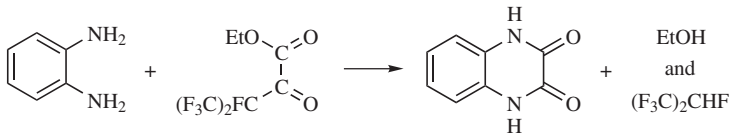
In contrast, 4-methyl-1,2-benzenediamine (**263**) and the same synthon (**261**) gave an inseparable 70 : 30 mixture of 3-amino-7-methyl- (**264**) and 3-amino-6-methyl-2(1*H*)-quinoxalinone (**265**) [EtOH, 25°C, >8 h: 77% (mixture)]; likewise analogous mixtures.[564,580]



(**263**) (**264**) (**265**)

1,2-Benzenediamine (**266**) and ethyl (perfluoroisobutyryl)formate (**267**) gave only 2,3(1*H*,4*H*)-quinoxalinedione (**268**) (MeCN, 0°C, ? h: 80%).[898]

Note: The synthon (**267**) might have been expected to react as a keto ester with 1,2-benzenediamine, but clearly the heptafluoropropane (**269**) is more easily lost than is water during the condensation.



(**266**) (**267**) (**268**) (**269**)

1.2.3.12. Using an Estero Amide, Nitrile, Acyl Halide, or Related Synthon

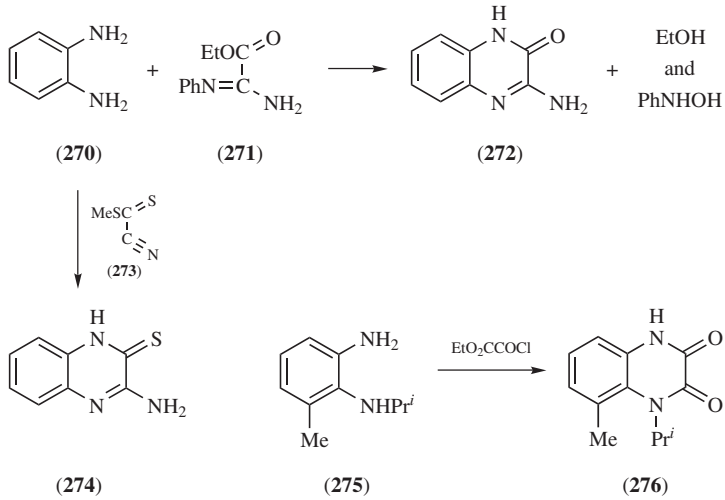
A majority of the few available examples in this broad category involve the use of equivalents to the foregoing synthons, as indicated in the following typical cases.

1,2-Benzenediamine (**270**) and the nitrone, ethyl 2-amino-2-(oxidophenylimino) acetate (**271**) (the equivalent of ethyl carbamoylformate) gave 3-amino-2(1*H*)-quinoxalinone (**272**) with loss of EtOH and *N*-phenylhydroxylamine (EtOH, trace AcOH, 20°C, ? h: 45%).[646]

The same substrate (**270**) and methyl cyano(dithioformate) (**273**) gave 3-amino-2(1*H*)-quinoxalinethione (**274**) (minimal detail: 41% after separation from a byproduct).[416]

2-Isopropylamino-3-methylaniline (**275**) and ethoxalyl chloride gave 1-isopropyl-8-methyl-2,3(1*H*,4*H*)-quinoxalinedione (**276**) ($EtPr^i_2N$, PhMe, −78°C, 1 h; then 0°C, 16 h; then reflux, 24 h: 45%);[729] several analogs were made similarly.[729,1016]

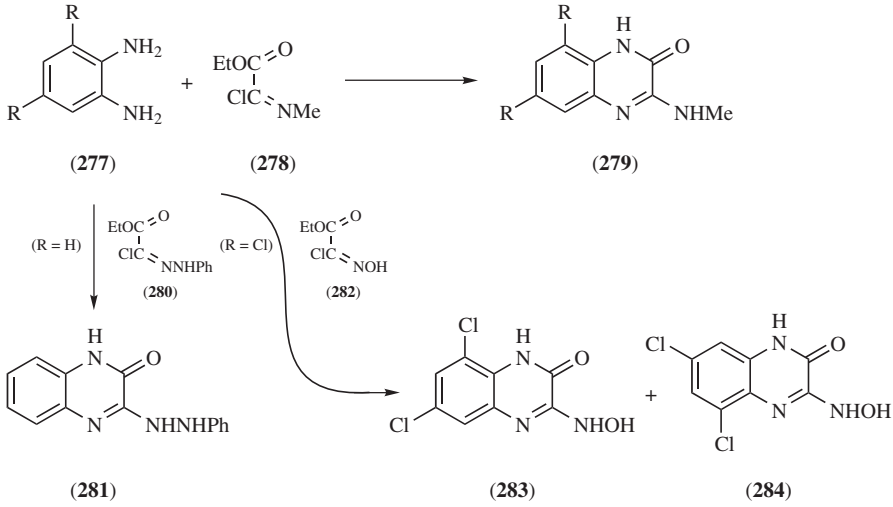
1,2-Benzenediamine (**277**, R = H) and ethyl 2-chloro-2-methylimino)acetate (**278**) gave 3-methylamino-2(1*H*)-quinoxalinone (**279**, R = H) (HCl gas, THF, 60°C→20°C, ~30 min: 71%);[669] the unsymmetric substrate, 3,5-dichloro-1,2-benzenediamine (**277**, R = Cl), and the same synthon



(**278**) should have given two isomeric products, but only 6,8-dichloro-3-methylamino-2(1*H*)-quinoxalinone (**279**, R = Cl) was isolated (as hydrochloride) (THF, 10°C→20°C, 1 day: 61%);[562] however, a related unsymmetric substrate did give an inseparable mixture of isomeric products.[562]

1,2-Benzenediamine (**277**, R = H) and ethyl 2-chloro-2-(phenylhydrazono)acetate (**280**) gave 3-(2-phenylhydrazino)-2(1*H*)-quinoxalinone (**281**) (Et_3N, EtOH, reflux, 3 h: 72);[879] analogs likewise.[516,879]

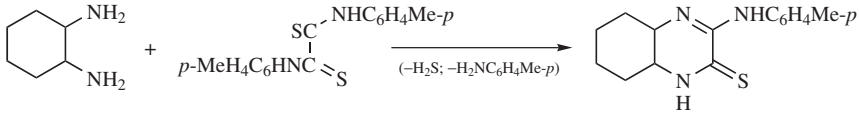
3,5-Dichloro-1,2-benzenediamine (**277**, R = Cl) and ethyl 2-chloro-2-(hydroxyimino)acetate (**282**) gave an apparently inseparable mixture of 6,8-dichloro- (**283**) and 5,7-dichloro-3-hydroxyamino-2(1*H*)-quinoxalinone (**284**) ($NaHCO_3$, EtOH–H_2O, 20°C, 24 h: 81% of the mixture).[562]



1.2.3.13. Using a Diamide (Oxamide), Amido Nitrile, or Related Synthon

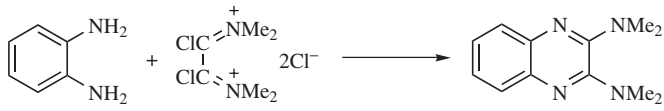
This is a very neglected category of cyclocondensation. However, the following examples indicate its potential utility.

1,3-Diaminocyclohexane (**285**) and *N*,*N*-di-*p*-tolyldithiooxamide (**286**) gave 3-*p*-toluidino-4a,5,6,7,8,8a-hexahydro-2(1H)-quinoxalinethione (**287**) (Me_2SO, 40°C, ? h: 72%; it is interesting that the two thioamide entitites reacted in different ways).[398]



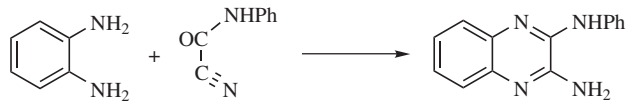
(**285**) (**286**) (**287**)

1,2-Benzenediamine (**288**) and the unstable oxamide equivalent (**289**), prepared in situ by chlorination of bis(dimethylamino)acetylene, gave 2,3-bis(dimethyl amino)quinoxaline (**290**) (no details).[31]



(**288**) (**289**) (**290**)

1,2-Benzenediamine (**291**) and *C*-cyanoformanilide (**292**) gave 3-anilino-2-quinoxalinamine (**293**) (probably EtOH, reflux, ~3 h: 70%).[603]

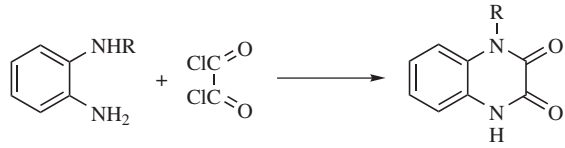


(**291**) (**292**) (**293**)

1.2.3.14. Using a Diacyl Dihalide (Oxalyl Halide) or Related Synthon

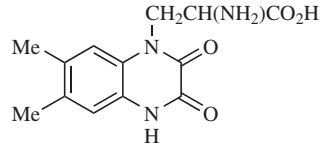
Like the preceding category, this is poorly represented in recent literature, although it has significant potential, as illustrated in the following examples.

1,2-Benzenediamine (**294**, R = H) and oxalyl chloride (**295**) gave 2,3(1*H*,4*H*)-quinoxalinedione (**296**, R = H) (*o*-$Cl_2C_6H_4$, 60°C, 30 min; then 130°C, 1 h: ?%);[713] likewise, *o*-(methylamino)aniline (**294**, R = Me) gave 1-methyl-2,3(1*H*,4*H*)-quinoxalinedione (**296**, R=Me), and other analogs were also so made.[713]



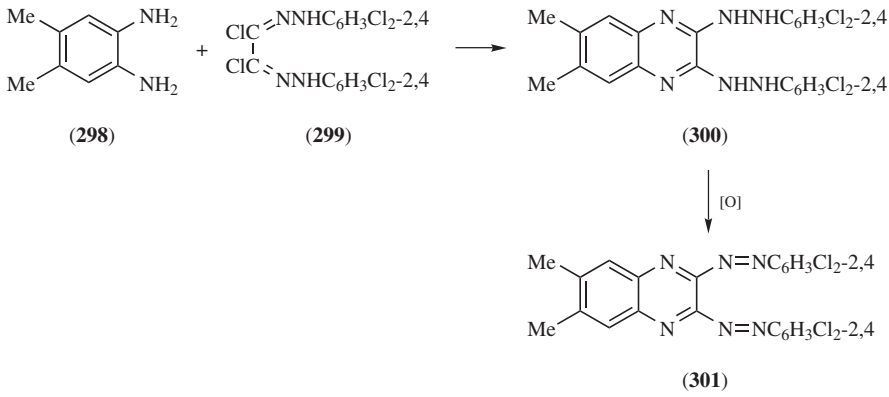
(**294**) (**295**) (**296**)

2-(2-Amino-2-carboxyethyl)amino-4,5-dimethylaniline and oxalyl chloride gave 1-(2-amino-2-carboxyethyl)-6,7-dimethyl-2,3(1*H*,4*H*)-quinoxalinedione (**297**) as hydrochloride (CH_2Cl_2, 0°C, ~30 min; then 20°C, 12 h; then 30°C, 6 h: 43%).[731]



(**297**)

4,5-Dimethyl-1,2-benzenediamine (**298**) and 1,2-dichloro-1,2-bis(2,4-dichlorophenylhydrazono)ethane (**299**) gave 2,3-bis[*N*'-(2,4-dichloeophenyl)hydrazino]-6,7-dimethylquinoxaline (**300**) (Et_3N, EtOH, reflux, 3 h: 90%), which was oxidized subsequently to afford 2,4-bis(2,4-dichlorophenylazo)-6,7-dimethylquinoxaline (**301**) [$(Fe_3CCO_2)_2$IPh, CH_2Cl_2, 20°C, 2 h: 81%].[578]



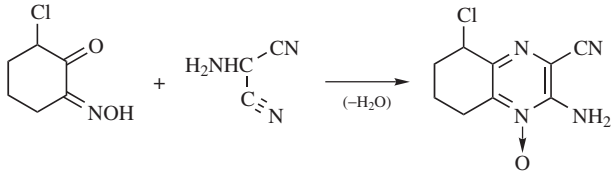
(**298**) (**299**) (**300**) (**301**)

Also other examples.[807,1103]

1.2.4. When the Synthon Supplies N1 + C2 + C3 of the Quinoxaline

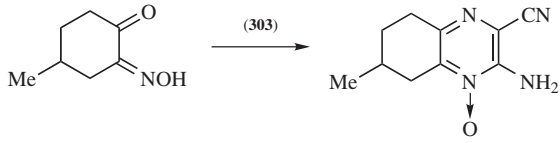
This type of cyclocondensation has not been developed to any extent. However, the following examples indicate that it could eventually become a valuable procedure.

2-Chloro-6-hydroxyiminocyclohexanone (**302**) (as hydrochloride) and α-aminomalononitrile (**303**) (as tosylate) gave 3-amino-8-chloro-5,6,7,8-tetrahydro-2-quinoxalinecarbonitrile 4-oxide (**304**) (Pr^iOH, 20°C, 18 h: 46%).[354]



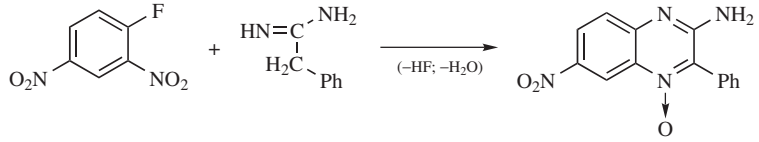
(**302**) (**303**) (**304**)

Likewise, 2-hydroxyimino-4-methylcyclohexanone (**305**) and the same synthon (**303**) gave 3-amino-6-methyl-5,6,7,8-tetrahydro-2-quinoxalinecarbonitrile 4-oxide (**306**) (Pr^iOH, 20°C, 48 h: 74%).[704]



(**305**) (**306**)

1-Fluoro-2,4-dinitrobenzene (**307**) and 2-phenylacetamidine (**308**) (liberated in situ) gave 6-nitro-3-phenyl-2-quinoxalinamine 4-oxide (**309**) (EtOH, reflux, 8 h: ~15%).[156]

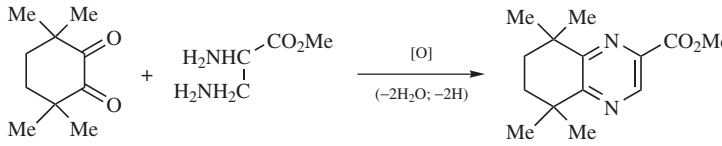


(**307**) (**308**) (**309**)

1.2.5. When the Synthon Supplies N1 + C2 + C3 + N4 of the Quinoxaline

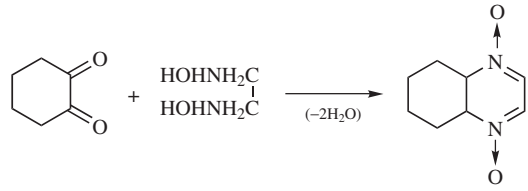
Although intrinsically unappealing, this category of synthesis has been used occasionally in several forms, especially with cyclohexane rather than benzene substrates. The following miscellaneous examples suggest that the procedure is surely worth further development.

3,3,6,6-Tetramethyl-1,2-cyclohexanedione (**310**) and methyl 2,3-diaminopropionate (**311**) (liberated in situ) gave methyl 5,5,8,8-tetramethyl-5,6,7,8,-tetrahydro-2-quinoxalinecarboxylate (**312**) [MeOH, molecular sieve (3Å), reflux, 5 h: 45%; note the spontaneous aerial (?) oxidation].[737]



(**310**) (**311**) (**312**)

1,2-Cyclohexanedione (**313**) and 1,2-bis(hydroxyamino)ethane (**314**) gave 4a,5,6,7,8,8a-hexahydroquinoxaline 1,4-dioxide (**315**) (formulated as the 2,3,5,6,7,8-hexahydro tautomer) (dilute HCl, 20°C, 3 h: 72%).[799]

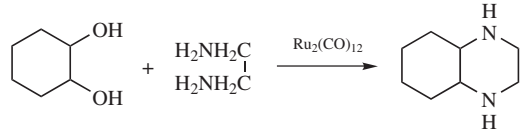


(**313**) (**314**) (**315**)

1,2-Cyclohexanedione (**316**) and ethyl 2-amidino-2-aminoacetate (**317**) (as hydrochloride) gave ethyl 3-amino-5,6,7,8-tetrahydro-2-quinoxalinecarboxylate (**318**) (H_2O–EtOH, AcONa, 10°C, 5 h: ? %).[519]

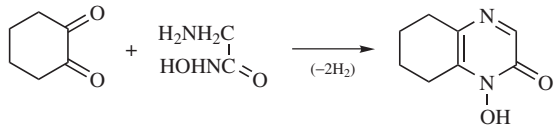
(**316**) (**317**) (**318**)

1,2-Cyclohexanediol (**319**) and ethylenediamine (**320**) gave decahydroquinoxaline (**321**) [$Ru_2(CO)_{12}PBu_3$, THF, 220°C, sealed, 1.5 h: 75%].[127]



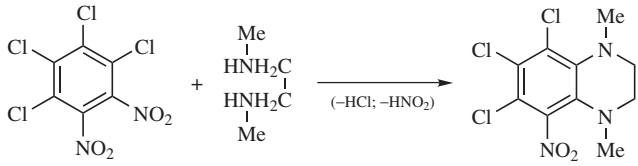
(**319**) (**320**) (**321**)

1,2-Cyclohexanedione (**322**) and 2-amino-*N*-hydroxyacetamide (**323**) gave 1-hydroxy-5,6,7,8-tetrahydro-2(1*H*)-quinoxalinone (**324**) (EtOH–H_2O, minimal detail: 41%).[618]



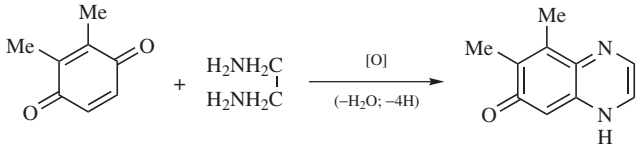
(**322**) (**323**) (**324**)

1,2,3,4-Tetrachloro-5,6-dinitrobenzene (**325**) and 1,2-bis(methylamino)ethane (**326**) gave 5,6,7-trichloro-1,4-dimethyl-8-nitro-1,2,3,4-tetrahydroquinoxaline (**327**) (PhMe, phase-transfer agent, reflux, 1 h: 55%; 20°C, 24 h: 52%);[543] also analogous condensations.[90]



(**325**) (**326**) (**327**)

2,3-Dimethyl-1,4-benzoquinone (**328**) and ethylenediamine (**329**) gave 7,8-dimethyl-6(4*H*)-quinoxalinone (**330**) (EtOH–CH_2Cl_2, 20°C, light exclusion: 35%; the required oxidation was probably provided by an excess of the quinone).[875]

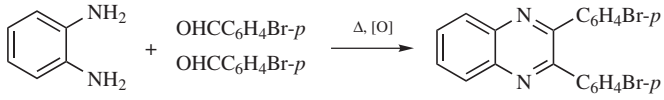


(**328**) (**329**) (**330**)

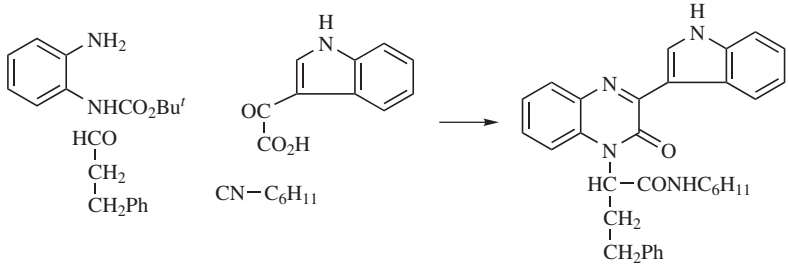
1.3. FROM A BENZENE SUBSTRATE WITH TWO OR MORE SYNTHONS

This category of primary synthesis is extremely rare in the quinoxaline series, although a few examples have been reported in recent literature. Thus a mixture of neat 1,2-benzenediamine (**331**) and an excess of *p*-bromobenzaldehyde heated at 350°C for ~5 min afforded (with aerial oxidation?) 2,3-bis(*p*-bromophenyl) quinoxaline (**332**) in 50% yield;[494] and analogs were made similarly but usually in poor to mediocre yield after separation from byproducts.[494] In addition, an

extraordinary one-pot reaction between a benzene substrate and no less than three synthons [*o*-(*tert*-butoxycarbonylamino)aniline, 3-oxaloindole, 3-phenylpropionaldehye, cyclohexane isocyanide; MeOH, 20°C, 24 h; evaporation; F_3CCO_2H, CH_2Cl_2, 20°C, 18 h] afforded 1-[1-(cyclohexylaminocarbonyl)-3-phenylpropyl]-3-(indol-3-yl)-2(1*H*)-quinoxalinone (**333**) in almost quantitative yield; several analogs were made similarly.[1088]



(**331**) (**332**)

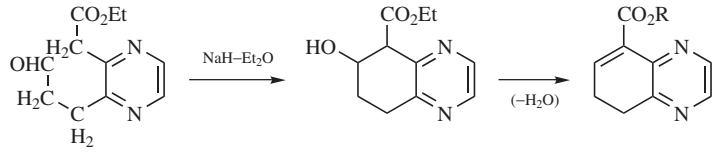


(**333**)

1.4. FROM A PYRAZINE SUBSTRATE WITH OR WITHOUT SYNTHON(S)

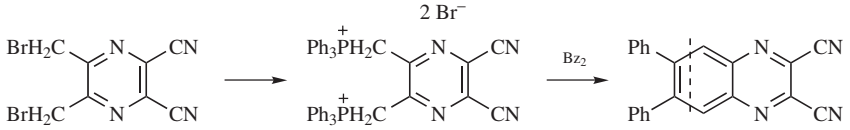
This potentially wide category of primary syntheses remains almost unutilized apart from the few examples here given.

2-Ethoxycarbonylmethyl-3-(2-formylethyl)pyrazine (**334**) (freshly liberated from its acetal) gave a separable mixture of ethyl 6-hydroxy-5,6,7,8-tetrahydro-5-quinoxalinecarboxylate (**335**); its dehydration product, ethyl 7,8-dihydro-5-quinoxalinecarboxylate (**336**, R = Et), and the hydrolysis product, 7,8-dihydro-2-quinoxalinecarboxylic acid (**336**, R = H) [NaH, Et_2O, 0°C, 2 h: 15%, 37%, and 37%, respectively; when the aqueous workup was carried out at 0°C, product **335** predominated].[246]



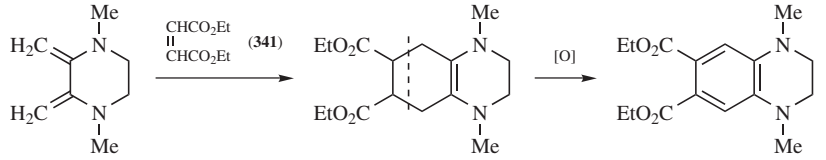
(**334**) (**335**) (**336**)

4,5-Bis(triphenylphosphoniomethyl)-2,3-pyrazinedicarbonitrile dibromide (**338**), prepared from the corresponding bis(bromomethyl) intermediate (**337**), reacted with benzil to afford 6,7-diphenyl-2,3-quinoxalinedicarbonitrile (**339**) (NaH, Me_2NCHO, 20°C→125°C, 9 h: 58%);[848] several analogs were made similarly.[848]



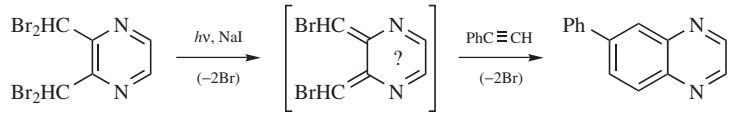
(**337**) (**338**) (**339**)

1,4-Dimethyl-2,3-dimethylenehexahydropyrazine (**340**) and diethyl fumarate (**341**) underwent a Diels–Alder reaction to give diethyl 1,4-dimethyl-1,2,3,4,5,6,7,8-octahydro-6,7-quinoxalinedicarboxylate (**342**) ($MeOBu^t$, −78°C→20°C, 48 h: 78%) and thence diethyl 1,4-dimethyl-1,2,3,4-tetrahydro-6,7-quinoxalinedicarboxylate (**343**) (PhH, air↓, 20°C, 26 h: 76%);[573] numerous octahydro and tetrahydro analogs were made similarly.[573]



(**340**) (**342**) (**343**)

2,3-Bis(dibromomethyl)pyrazine (**344**) and ethynylbenzene gave 6-phenylquinoxaline (**346**), possibly via the unisolated intermediate (**345**) (reactants, NaI, little Me_2NCHO, microwave *hν*, open vessel, 20°C→90°C, 15 min: 38%); prop-1-ynylbenzene or 1-ethynylnaphthalene likewise gave 6-methyl-7-phenylquinoxaline (43%) or 6-(naphthalen-1-yl)quinoxaline (41%), respectively,[1112]



(**344**) (**345**) (**346**)

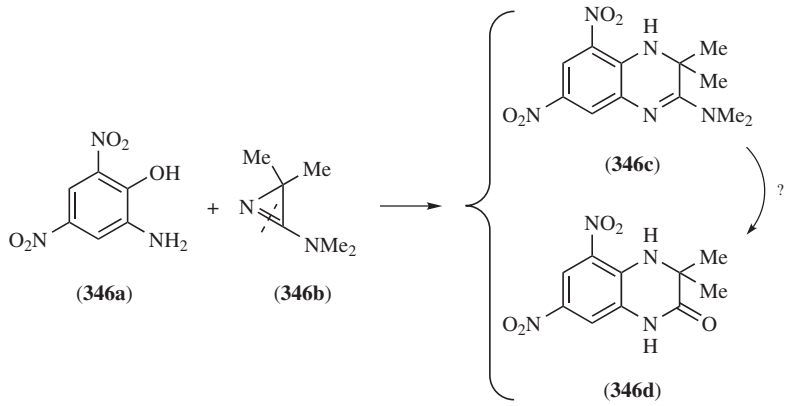
1.5. FROM OTHER HETEROMONOCYCLIC SUBSTRATES/SYNTHONS

Heteromonocyclic compounds other than pyrazines may be used as substrates or synthons for the primary synthesis of quinoxalines. All such syntheses are covered

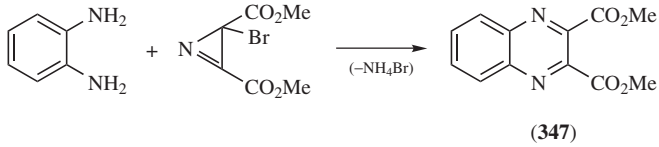
in the following subsections, which are arranged alphabetically according to the name of the fully unsaturated heterocyclic system, even when a partially or fully reduced system is involved. Cyclic monosaccharides are considered as heterocycles here.

1.5.1. Azirines as Substrates/Synthons

Recent examples of this synthesis are of two types. The first involves condensation of the activated phenol, 2-amino-4,6-dinitrophenol (**346a**) with 2-dimethylamino-3,3-dimethyl-3*H*-azirine (**346b**) (in MeCN, 0°C→20°C, A, 24 h) to afford a separable mixture of four products, one of which was 2-dimethylamino-3,3-dimethyl-5,7-dinitro-3,4-dihydroquinoxaline (**346c**) (∼20% yield) and another its hydrolysis product, 3,3-dimethyl-5,7-dinitro-3,4-dihydro-2(1*H*)-quinoxalinone (**346d**) (∼8%);[56] the mechanism of such condensations has been discussed.[56,1052]



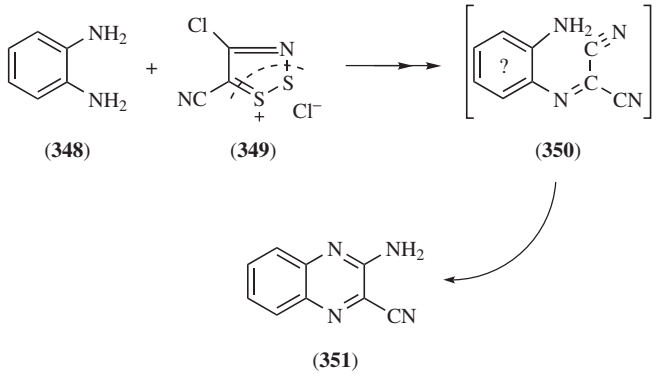
The second type is examplified in the condensation of 1,2-benzenediamine with dimethyl 3-bromo-3*H*-azirine-2,3-dicarboxylate to give dimethyl 2,3-quinoxalinedicarboxylate (**347**) (Me_2NCHO, 20°C, ultrasound, 2 h: 69%); analogs were made likewise.[1101]



1.5.2. 1,2,3-Dithiazol-1-iums as Substrates/Synthons

The sole recent example of this synthesis involved the complex reaction of 1,2-benzenediamine (**348**) with 4-chloro-5-cyano-1,2,3-dithiazol-1-ium chloride (**349**)

(in CH_2Cl_2, "Hunig's base," $-78°C \rightarrow 20°C$) to furnish 3-amino-2-quinoxalinecarbonitrile (**351**) in 12% yield; a possible reaction mechanism via the unisolated intermediate (**350**) was proposed.[560]



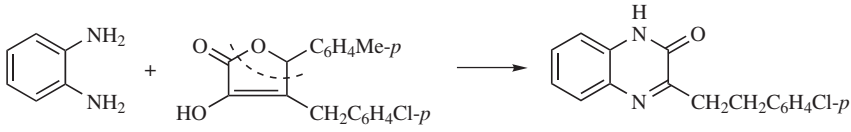
(**348**) (**349**) (**350**)

(**351**)

1.5.3. Furans as Substrates/Synthons (*H* 293)

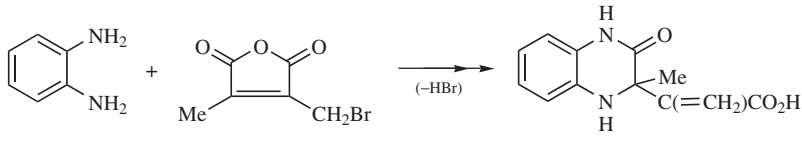
Many furanones (including furanose carbohydrates) have been used as synthons with 1,2-benzenediamines to afford quinoxaline derivatives. The following examples illustrate the main types of such cyclocondensation reactions.

1,2-Benzenediamine (**352**) and 4-*p*-chlorobenzyl-3-hydroxy-5-*p*-tolyl-2,5-dihydro-2-furanone (**353**) gave 3-(*p*-chlorophenethyl)-2(1*H*)-quinoxalinone (**354**) with loss of *p*-methylbenzaldehyde (isolated as its phenylhydrazone) (EtOH, trace AcOH, 98°C, 4 h: 65%);[89] analogs likewise.[89,211,565,830,834]



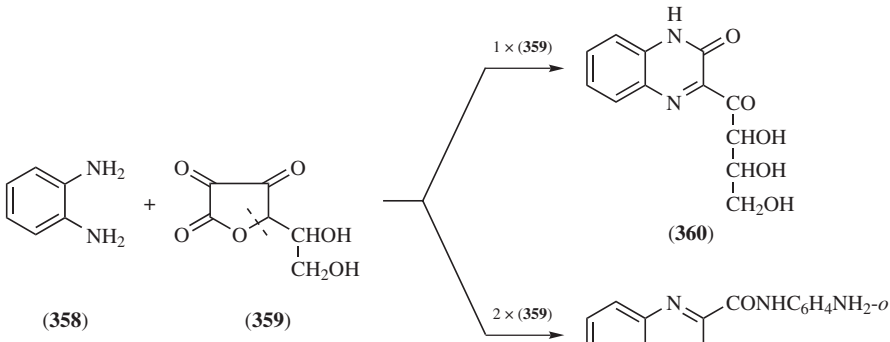
(**352**) (**353**) (**354**)

1,2-Benzenediamine (**355**) and 3-bromomethyl-4-methyl-2,5-dihydro-2,5-furandione (2-bromomethyl-3-methylmaleic anhydride: **356**) gave 3-(1-carboxyvinyl)-3-methyl-3,4-dihydro-2(1*H*)-quinoxalinone (**357**) with loss of hydrogen bromide ($CHCl_3$, $-15°C \rightarrow 20°C$, 4 h: 86%); a rational mechanism was proposed.[625]

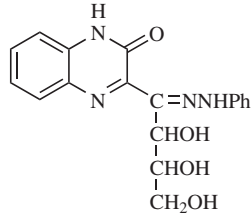


(**355**) (**356**) (**357**)

1,2-Benzenediamine (**358**) and 5-(1,2-dihydroxyethyl)tetrahydro-2,3,4-furanetrione (**359**) (prepared in situ by oxidation of ascorbic acid with *p*-benzoquinone) gave either 3-(2,3,4-trihydroxybutyryl)-2(1*H*)-quinoxalinone (**360**) [substrate (**358**) (1 mol), H_2O, 20°C, 24 h: ~60% (?)][911,cf. 612] or *N*-(*o*-aminophenyl)-3-(1,2,3-trihydroxypropyl)-2-quinoxalinecarboxamide (**361**) [substrate (**358**) (2 mol), MeOH, 40°C, 2 h: ~65%].[914,cf. 259]



In a somewhat similar way, the same reagents (**358** and **359**) in equimolar proportions followed by treatment with phenylhydrazine afforded 3-(2,3,4-trihydroxy-1-phenylhydrazonobutyl)-2(1*H*)-quinoxalinone (**362**) directly (71%);[916] analogues likewise.[912,916]



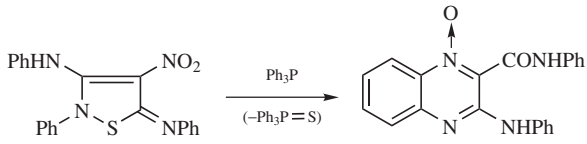
(**362**)

Also other examples.[301,399,545,612,952]

1.5.4. Isothiazoles as Substrates/Synthons

Although of more interest than utility, the desulfurization of certain isothiazoles with triphenylphosphine leads to separable mixtures from which quinoxalines have

been isolated in low yield. For example, 3-anilino-2-phenyl-5-phenylimino-4-nitro-2,5-dihydroisothiazole (**363**) with triphenyl phosphine in chloroform under nitrogen at 0°C→20°C during 90 min gave (after prolonged separation processes) 3-anilino-2-quinoxalinecarboxanilide 1-oxide (**364**) in 10% yield.[49] 3-Anilino-*N*-(*p*-nitrophenyl)-2-quinoxalinecarboxamide 1-oxide (9%) and several diverse analogs (in even lower yield) were made similarly from appropriate isothiazoles.[49] A rational mechanism has been proposed.[49]

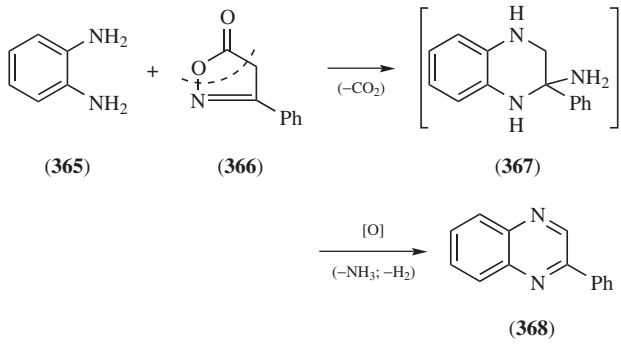


(**363**) (**364**)

1.5.5. Isoxazoles as Substrates/Synthons

Although little used, this type of synthesis may be employed in two different ways to produce quinoxalines from *o*-phenyldiamines as substrates. Examples follow.

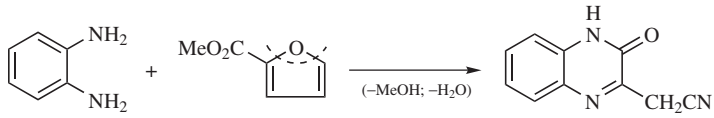
1,2-Benzenediamine (**365**) and 3-phenyl-4,5-dihydro-5-isoxazolone (**366**) gave 2-phenylquinoxaline (**368**), probably via the tetrahydro intermediate (**367**) (MeCN, reflux, 4 h: 65%);[446] several substituted-phenyl analogs were prepared similarly and in comparable yields.[446] When an unsymmetrically substituted benzenediamine was used, two isomeric products were expected, but only one could be detected in each such case tried.[446]



(**365**) (**366**) (**367**)

(**368**)

1,2-Benzenediamine (**369**) and methyl 5-isoxazolecarboxylate (**370**) gave 3-cyanomethyl-2(1*H*)-quinoxalinone (**371**) (Me_2SO, reflux, 5 min: 70%).[76]

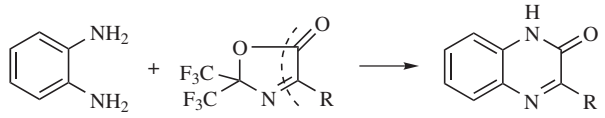


(**369**) (**370**) (**371**)

Also other examples.[435]

1.5.6. Oxazoles as Substrates/Synthons

Only one procedure in this category emerged from the present survey. Thus treatment of 1,2-benzenediamine (**372**) with 3,3-bis(trifluoromethyl)-5-oxazolinone (**373**, R = H) in ethyl acetate containing a trace of acetic acid at room temperature for a short time afforded 2(1*H*)-quinoxalinone (**374**, R = H) in 92% yield;[695] 3-methyl- (**374**, R = Me), 3-isopropyl- (**374**, R = Pr^i), 3-phenyl- (**374**, R = Ph), and 3-benzyl-2(1*H*)-quinoxalinone (**374**, R = CH_2Ph) were made similarly in 60–80% yield.[695]

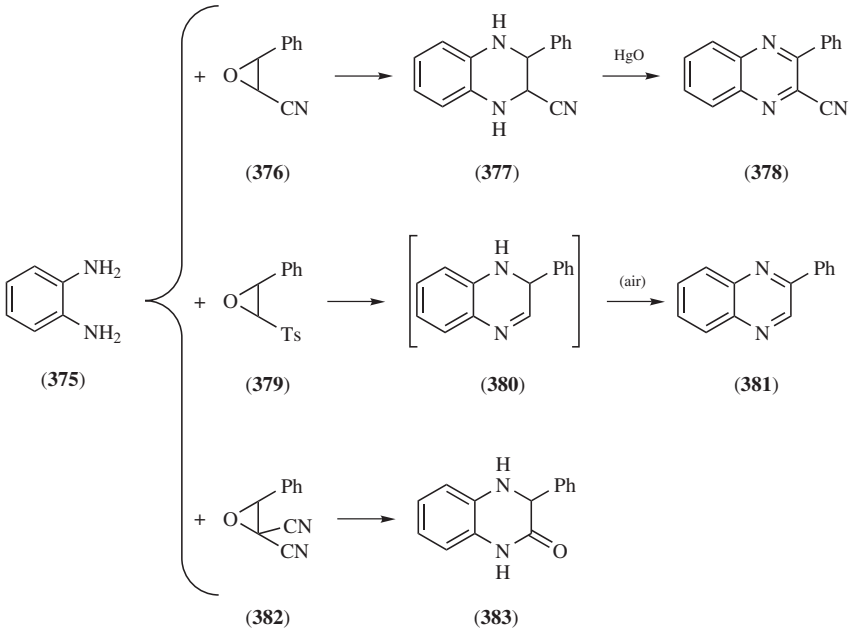


(**372**) (**373**) (**374**)

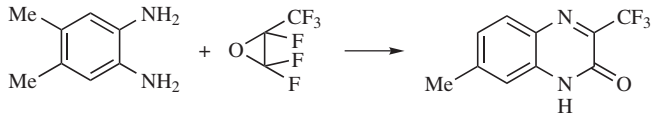
1.5.7. Oxirenes as Substrates/Synthons

Although oxirenes have not been used as such, their reduced analogs (oxiranes or ethylene oxides) have been employed quite widely to make hydroquinoxalines (or sometimes quinoxalines by subsequent oxidation, spontaneous or otherwise). Such reactions are illustrated in the following examples.

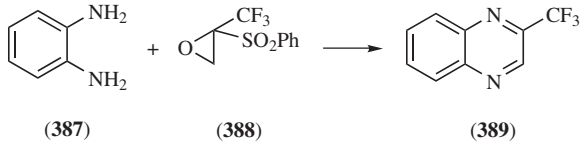
1,2-Benzenediamine (**375**) with 3-phenyl-2-oxiranecarbonitrile (**376**) gave 3-phenyl-1,2,3,4-tetrahydro-2-quinoxalinecarbonitrile (**377**) (EtOH, reflux, N_2, 3 h: 92%) and thence 3-phenyl-2-quinoxalinecarbonitrile (**378**) (HgO, EtOH, reflux, 75 min: 64%); with 2-phenyl-3-tosyloxirane (**379**) gave 2-phenylquinoxaline (**381**), probably by spontaneous aerial oxidation of the 1,2-dihydro derivative (**380**) (Me_2NCHO, 90°C, N_2, 3 h: 66%); or with 3-phenyl-2,2-oxiranedicarbonitrile (**382**) gave 3-phenyl-3,4-dihydro-2(1*H*)-quinoxalinone (**383**) (EtOH, reflux, N_2, 4 h: 60%).[157] Several analogs were made similarly, and a rational explanation of these behavioral variations may be found in the original paper.[157]



4,5-Dimethyl-1,2-benzenediamine (**384**) and 2,2,3-trifluoro-3-trifluoromethyloxirane (**385**) gave 3-trifluoromethyl-2(1*H*)-quinoxalinone (**386**) ($NaHCO_3$, CH_2Cl_2–Et_2O, 23°C, sealed, 12 h: 78%);[192] analogs similarly.[1001]



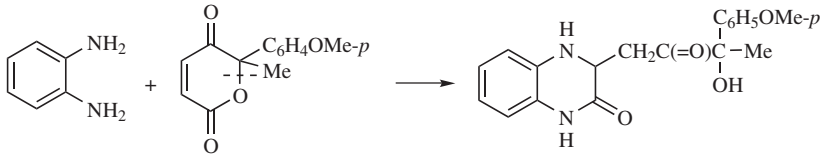
1,2-Benzenediamine (**387**) and 2-phenylsulfonyl-2-trifluoromethyloxirane (**388**) gave 2-trifluoromethylquinoxaline (**389**) (EtOH, 20°C, 2 h, then reflux, 16 h: 45%).[901]



Also many other examples involving other derivatives of oxirane as synthones.[376,378,510,657,859,1061,1089]

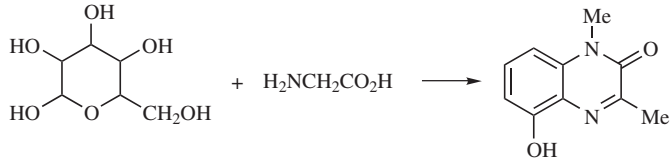
1.5.8. Pyrans as Substrates/Synthons

At least two derivatives of pyran have been used for the primary synthesis of quinoxalines. Thus *o*-phenylenediamine (**390**) and 6-(*p*-methoxyphenyl)-6-methyl-5,6-dihydro-2*H*-pyran-2,5-dione (**391**) in methylene chloride at 20°C open to the air for 48 h gave 3-[2-hydroxy-2-(*p*-methoxyphenyl)propionyl]methyl-3,4-dihydro-2(1*H*)-quinoxalinone (**392**) (as a mixture of two stereoisomers) in 92% yield;[488] the 3,4,4a,5,6,7,8,8a-octahydro analog was made similarly from 1,2-diaminocyclohexane (91% of two separable stereoisomers).[488]



(**390**) (**391**) (**392**)

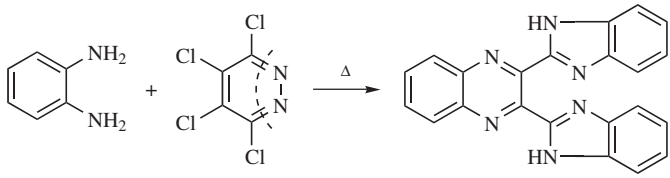
In a less straightforward way, D-glucose (**393**) underwent a Maillard-type reaction with an excess of glycine (**394**) under microwave irradiation to afford 5-hydroxy-1,3-dimethyl-2(1*H*)-quinoxalinone (**395**) as a major product,[926] Repetition with labeled reactants suggested that the product contained six carbon atoms from the sugar and four from the amino acid; on this evidence, a detailed mechanism has been postulated.[926]



(**393**) (**394**) (**395**)

1.5.9. Pyridazines as Substrates/Synthons

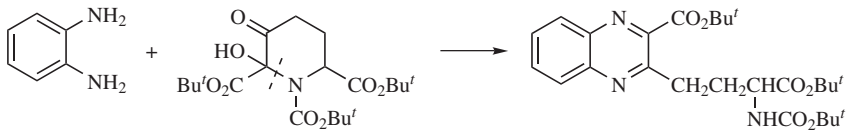
Only one example in this category has been described in recent years (as of 2003). Treatment of *o*-phenylenediamine (**396**) with 3,4,5,6-tetrachloropyridazine (**397**) in *N*-methylpyrrolidine at 115°C for 17 h gave a separable mixture of products, one of which was 2,3-bis(benzimidazol-2-yl)quinoxaline (**398**) (unstated yield).[666] The structure (**398**) was confirmed by X-ray analysis,[835,1053] and a mechanism for its formation was suggested.[835]



(**396**) (**397**) (**398**)

1.5.10. Pyridines as Substrates/Synthons

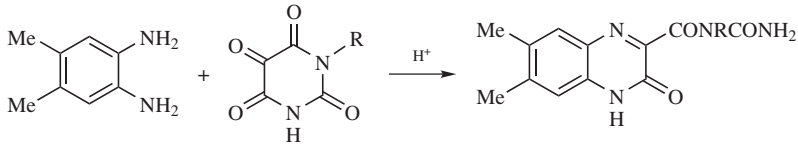
The sole recent example in this category is the condensation (in hot aqueous ethanolic sodium hydrogen carbonate) of *o*-phenylenediamine (**399**) with tri-*tert*-butyl 2-hydroxy-3-oxo-1,2,6-piperidinetricarboxylate (**400**) to give *tert*-butyl 3-[3-(*tert*-butoxycarbonyl)-3-(*tert*-butoxycarbonylamino)propyl]-2-quinoxalinecarboxylate (**401**) in 87% yield.[276]



(**399**) (**400**) (**401**)

1.5.11. Pyrimidines as Substrates/Synthons

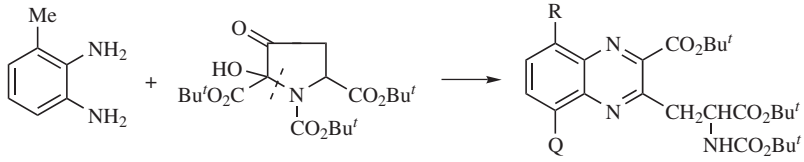
The unlikely transformation of a pyrimidine into a quinoxaline has, indeed, been reported. Thus 4,5-dimethyl-1,2-benzenediamine (**402**) and alloxan (**403**, R = H) under acidic conditions gave 6,7-dimethyl-3-ureidocarbonyl-2(1*H*)-quinoxalinone (**404**, R = H) (~30%: see original for details); *N*-methylalloxan (**403**, R = Me) likewise gave 6,7-dimethyl-3-(*N*-methylureido)carbonyl-2(1*H*)-quinoxalinone (**404**, R = Me) in ~50% yield.[868] Such condensations gave improved yields under solid-state conditions.[1065]



(**402**) (**403**) (**404**)

1.5.12. Pyrroles as Substrates/Synthons

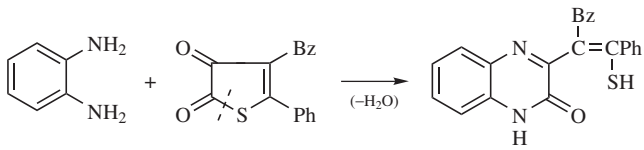
This category is exemplified, albeit poorly, in the reaction of 3-methyl-1,2-benzenediamine (**405**) with tri-*tert*-butyl 2-hydroxy-3-oxo-1,2,5-pyrrolidinetricarboxylate (**406**) in aqueous ethanolic sodium hydrogen carbonate under reflux for ~3 h. This gave, as minor products, an inseparable mixture (in ~9% yield) of *tert*-butyl 3-[2-(*tert*-butoxycarbonyl)-2-(*tert*-butoxycarbonylamino)ethyl]-5-methyl-2-quinoxalinecarboxylate (**407**, Q = Me, R = H) and its 8-methyl isomer (**407**, Q = H, R = Me).[276]



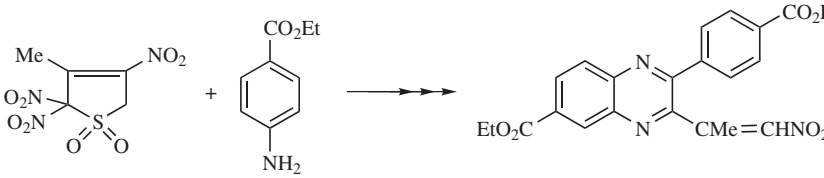
(**405**) (**406**) (**407**)

1.5.13. Thiophenes as Substrates/Synthons

This category is represented in the facile reaction of *o*-phenylenediamine (**408**) with 4-benzoyl-5-phenyl-2,3-dihydro-2,3-thiophenedione (**409**) (in toluene at 20°C for 30 min) to afford 3-(α-benzoyl-β-mercaptostyryl)-2(1*H*)-quinoxalinone (**410**) in 98% yield;[744] also in the complicated reaction of 3-methyl-2,2,4-trinitro-2,5-dihydrothiophene 1,1-dioxide (**411**) with 2 equiv of ethyl 4-aminobenzoate (**412**) (in acetonitrile but no further details) to give ethyl 2-(*p*-ethoxycarbonylphenyl)-3-(1-methyl-2-nitrovinyl)-6-quinoxalinecarboxylate (**413**) in 51% yield.[831] Several analogs were made similarly.[831]



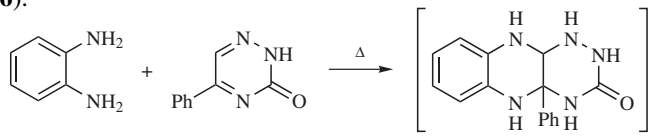
(**408**) (**409**) (**410**)



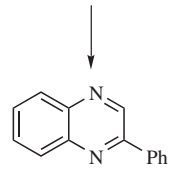
(**411**) (**412**) (**413**)

1.5.14. 1,2,4-Triazines as Substrates/Synthons

When *o*-phenylenediamine (**414**) was heated with 5-phenyl-1,2,4-triazin-3(2*H*)-one (**415**) (in ethanolic hydrogen chloride under reflux for 5 h), 2-phenylquinoxaline (**417**) was obtained in 34% yield; the reaction is said to proceed via the tricyclic adduct (**416**).[906]



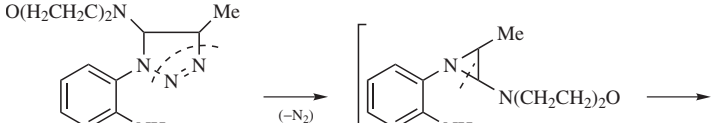
(**414**) (**415**) (**416**)



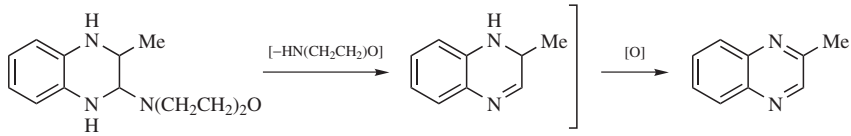
(**417**)

1.5.15. 1,2,3-Triazoles as Substrates/Synthons

This could develope into a useful unambiguous primary synthesis for simple quinoxalines; the starting triazoles are reasonably accessible, and subsequent steps can be done in one pot to afford good yields. For example, 1-(*o*-aminophenyl)-4-methyl-5-morpholino-4,5-dihydro-1,2,3-triazole (**418**) was heated in refluxing toluene for 1 h, and the crude solid from evaporation was then stireed with dichlorodicyanobenzoquinone in THF for ∼5 h to give 2-methylquinoxaline (**422**) in 89% yield; the mechanism via intermediates (**419–421**) is well based.[549] Appropriately substituted triazoles gave several analogous quinoxalines in comparable yields.[549]



(**418**) (**419**)



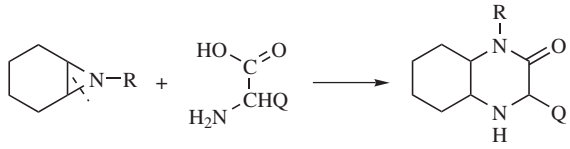
(**420**) (**421**) (**422**)

1.6. FROM HETEROBICYCLIC SUBSTRATES/SYNTHONS

Heterobicyclic compounds are important substrates (or synthons) for the primary synthesis of quinoxalines. Such procedures are arranged alphabetically here according to the system name of each substrate/synthon so used.

1.6.1. 7-Azabicyclo[4.1.0]heptanes as Substrates/Synthons

Although useful, this synthesis of reduced quinoxalines has not been fully developed yet. 7-Azabicyclo[4.1.0]heptane (**423**, R = H) and glycine (**424**, Q = H) in refluxing aqueous ammonium chloride for 90 min gave octahydro-2(1*H*)-quinoxalinone (**425**, Q = R = H) in 40% yield.[459] Similar treatment of 7-methyl-7-azabicyclo[4.1.0]heptane (**423**, R = Me) gave 1-methyloctahydro-2(1*H*)-quinoxalinone (**425**, Q = H, R = Me) in 62% yield; and 7-methyl-7-azabicyclo[4.1.0] heptane (**423**, R = Me) with L-alanine (**424**, R = Me) in refluxing aqueous ammonium chloride for 16 h gave two separable diastereoisomers of 1,3-dimethyloctahydro-2(1*H*)-quinoxalinone (**425**, Q = R = Me), isolated as hydrochlorides in 26% and 27% yields, respectively.[457]

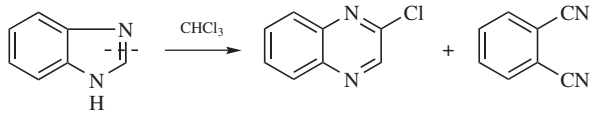


(**423**) (**424**) (**425**)

1.6.2. Benzimidazoles as Substrates/Synthons

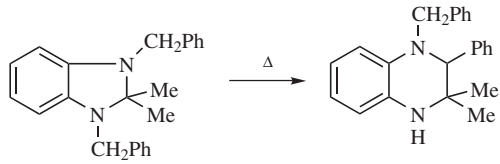
The ring expansion of benzimidazoles to afford qunoxalines has been done in several ways, mostly of little preparative value. They are illustrated in the following examples.

Benzimidazole (**426**) and chloroform gave a separable (?) 9 : 1 mixture of 2-chloroquinoxaline (**427**) and 1,2-benzenedicarbonitrile (pthalonitrile: **428**) (vapors, ~400°C, N_2, no details: ~50% of the mixture).[836]



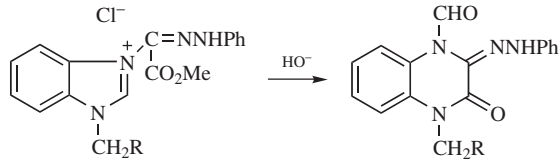
(**426**) (**427**) (**428**)

1,3-Dibenzyl-2,2-dimethyl-2,3-dihydrobenzimidazole (**429**) gave 1,4-dibenzyl-2,2-dimethyl-3-phenyl-1,2,3,4-tetrahydroquinoxaline (**430**) (neat, 200°C, sealed, ? h: 11% after separation from benzaldehyde; mechanism proposed).[682]



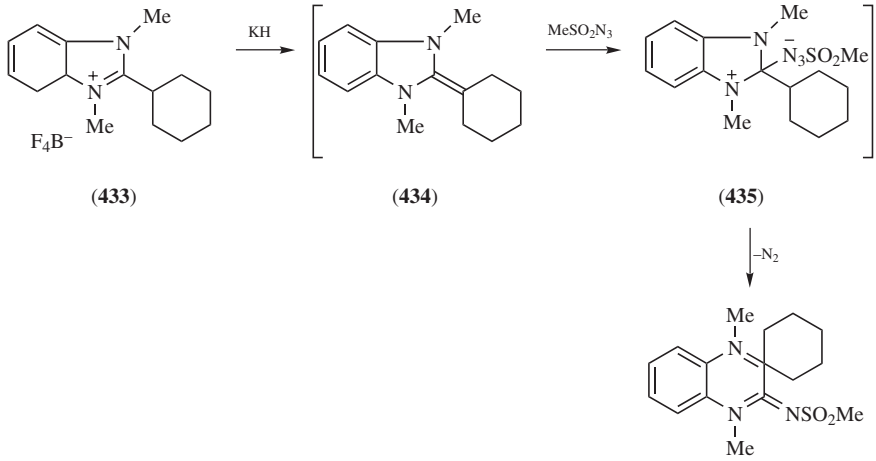
(**429**) (**430**)

1-(1-Hydrazono-1-methoxycarbonylmethyl)-3-methylbenzimidazol-1-ium chloride (**431**, R = H) gave 4-methyl-3-oxo-2-phenylhydrazono-1,2,3,4-tetrahydro-1-quinoxalinecarbaldehyde (**432**, R = H) (NaOH, EtOH–H_2O, 20°C, 12 h: 71%); the 4-benzyl analog (**432**, R = Ph) (50%) was made similarly.[516]



(**431**) (**432**)

2-Cyclohexyl-1,3-dimethylbenzimidazolium trifluoroborate (**433**) gave 3-(methanesulfonyl)imino-1,4-dimethyl-1,2,3,4-tetrahydroquinolaline-2-spirocyclohexane (**436**), via the well-established structures (**434** and **435**) [KH, THF, 20°C, 24 h; then $MeSO_2N_3\downarrow$, 20°C, 1 h: 37% after separation from a major byproduct].[1032]



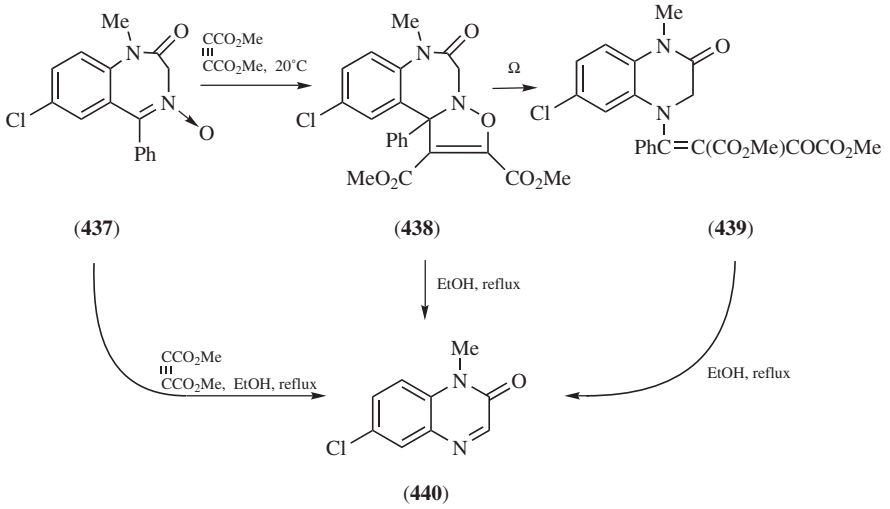
(**433**) (**434**) (**435**)

(**436**)

Also other examples.[341,577]

1.6.3. 1,4-Benzodiazepines as Substrates/Synthons (*E* 264)

Only one procedure has been reported recently within this category. Thus 7-chloro-1-methyl-5-phenyl-2,3-dihydro-1*H*-benzodiazepin-2-one 4-oxide (**437**) with dimethyl acetylenedicarboxylate in methylene chloride at 20°C for 3 days gave a separable mixture of the primary tricyclic adduct, dimethyl 10-chloro-6-oxo-11b-phenyl-5,6,7,11b-tetrahydroisoxazolo[2,3-*d*][1,4]benzodiazepine-1,2-dicarboxylate (**438**), and its rearrangement product, 6-chloro-4-(2-methoxalyl-2-methoxycarbonyl-1-phenylvinyl)-1-methyl-3,4-dihydro-2(1*H*)-quinoxalinone (**439**); each product afforded 6-chloro-1-methyl-2(1*H*)-quinoxalinone (**440**) on refluxing in ethanol (see also Section 1.7.13).[585] However, the final quinoxaline (**440**) was best obtained in ~75% yield) by simply heating the initial substrate (**437**) and dimethyl acetylenedicarboxylate in refluxing ethanol for 12 h.[585] The dimethyl analog, 6-chloro-2(1*H*)-quinoxalinone, was prepared in ~30% yield by a similar process.[585]

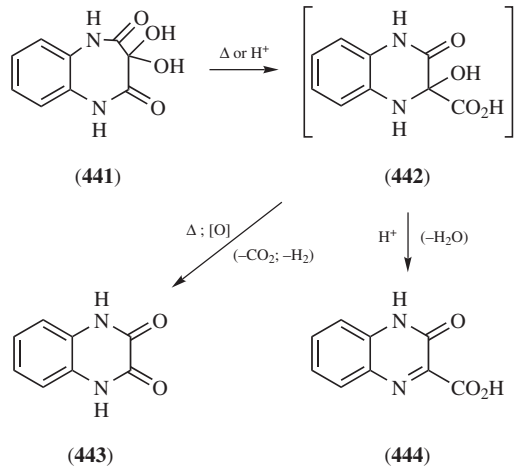


1.6.4. 1,5-Benzodiazepines as Substrates/Synthons

The ring contraction of 1,5-benzodiazepines to quinoxalines may yet prove a reasonable primary synthetic route, but current examples (mainly pyrolyses) are more interesting than useful.

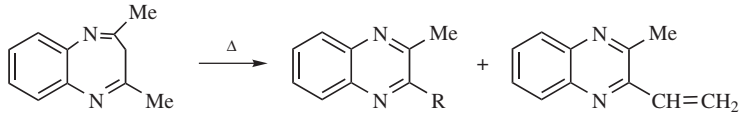
3,3-Dihydroxy-2,3,4,5-tetrahydro-1*H*-benzodiazepine-2,4-dione (**441**) gave 2,3-(1*H*,4*H*)-quinoxalinedione (**443**) (xylene, reflux, 4 h: 17% after purification) or 3-oxo-3,4-dihydro-2-quinoxalinecarboxylic acid (**444**) (2M HCl, reflux, 15 min: 58%); both products appear to have come from the intermediate

dihydroquinoxaline (**442**): the first by loss of CO_2 with aerial oxidation; the second by loss of H_2O).[217]



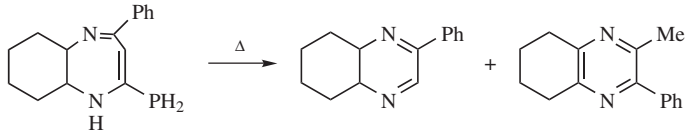
(**441**) (**442**) (**443**) (**444**)

2,4-Dimethyl-1,5-benzodiazepine, formulated as its 3*H* tautomer (**445**), underwent vapor-phase pyrolysis (850°C, 0.02 mmHg, 15 min) to give a mixture from which three quinoxalines were isolated: 2,3-dimethyl- (**446**, R = Me) (7%), 2-ethyl-3-methyl- (**446**, R = Et) (10%), and 2-methyl-3-vinylquinoxaline (**447**) (1%).[659]



(**445**) (**446**) (**447**)

2,4-Diphenyl-5a,6,7,8,9,9a-hexahydro-1*H*-benzodiazepine (**448**) underwent vapor-phase pyrolysis (~750°C but no further details) to give 2-phenyl-5,6,7,8-tetrahydroquinoxaline (**449**) (46%) and 2,4-diphenyl-5,6,7,8-tetrahydroquinoxaline (**450**) (4%).[111]



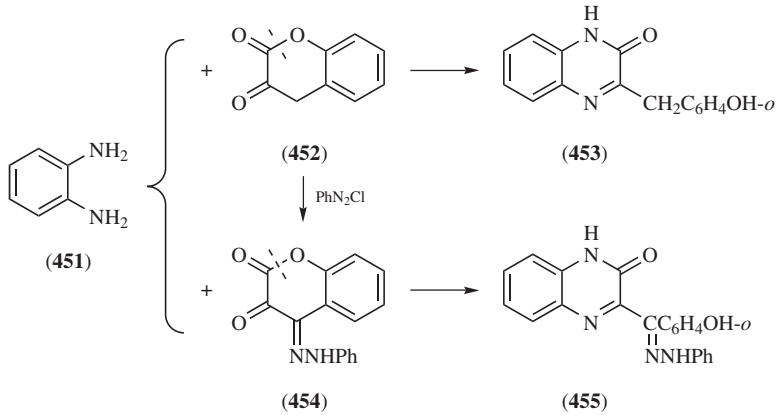
(**448**) (**449**) (**450**)

1.6.5. 1-Benzopyrans (Chromenes) as Substrates/Synthons

Appropriate 1-benzopyrans can undergo ring fission and condensation with 1,2-benzenediamines to afford 3-*o*-hydroxybenzyl-2(1*H*)-quinoxalinones or related products. The following examples illustrate this somewhat specialized procedure.

1,2-Benzenediamine (**451**) and 3,4-dihydro-2*H*-1-benzopyran-2,3-dione (**452**) gave 3-*o*-hydroxybenzyl-2(1*H*)-quinoxalinone (**453**) (1M NaOH, 100°C, 15 min: 84%; EtOH, reflux, 1 h: 59%; or AcOH–H_2O, 100°C, 1 h: 43%).[240]

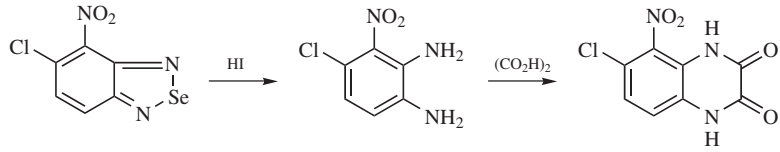
The same substrate (**451**) and 4-phenylhydrazono-3,4-dihydro-2*H*-1-benzopyran-2,3-dione (**454**) [prepared from the dione (**452**) with benzenediazonium chloride] gave 3-(*o*-hydroxy-α-phenylhydrazonobenzyl)-2(1*H*)-quinoxalinone (**455**) (EtOH–AcOH, reflux, 90 min: 80%).[233]



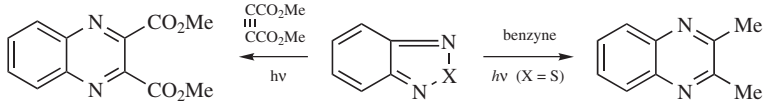
1.6.6. 2,1,3-Benzoselena(or thia)diazoles as Substrates/Synthons

Although derivatives of 2,1,3-benzoxadiazole have been used extensively to make quinoxalines (see Section 1.6.7), the corresponding selena and thia systems have been paid scant attention for that purpose. However, 5-chloro-4-nitro-2,1,3-benzoselenadiazole (**456**) has been used as a convenient source of 4-chloro-3-nitro-1,2-benzenediamine (**457**) (HCl + HI, 20°C, 2 h: 88%), which was then converted into 6-chloro-5-nitro-2,3(1*H*,4*H*)-quinoxalinedione (**458**) (oxalic acid, 2M HCl, reflux, 2.5 h: 23%).[1045] In addition, irradiation of 2,1,3-benzoselenadiazole (**460**, X = Se) or 2,1,3-benzothiadiazole (**460**, X = S) with dimethyl acetylenedicarboxylate afforded, among other products, dimethyl 2,3-quinoxalinedicarboxylate (**459**)

in 6% or a trace, respectively;[91,264,1054] and the thiasubstrate (**460**, X = S) with benzyne likewise gave 2,3-dimethylquinoxaline (**461**) in 13% yield.[91]



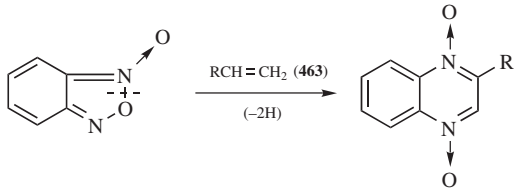
(**456**) (**457**) (**458**)



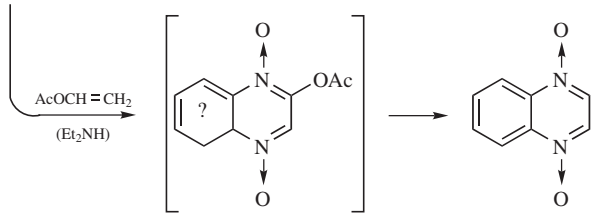
(**459**) (**460**) (**461**)

1.6.7. 2,1,3-Benzoxadiazoles as Substrates/Synthons (*E* 35)

There is an extensive literature on the use of 2,1,3-benzoxadiazole 1-oxide [often called *benzofuroxan*(*e*) (BFO) (**462**)] as a substrate for the primary synthesis of quinoxaline 1,4-dioxides and occasionally quinoxaline mono-*N*-oxides or even simple quinoxalines. Very few substituted derivatives of the parent substrate (**462**) have been employed in recent years. The general mechanism clearly involves a fission (usually amine-catalyzed) of the oxadiazole ring followed by reaction with an ancillary synthon. The following examples are divided according to the type of synthon employed.



(**462**) (**464**)



(**465**)

Simple Alkenes as Synthons

2,1,3-Benzoxadiazole 1-oxide (**462**) and styrene (**463** R = Ph) gave 2-phenylquinoxaline 1,4-dioxide (**464**, R = Ph) ($CHCl_3$, reflux, >30 h: 43%); 2-*p*-methoxyphenylquinoxaline 1,4-dioxide (**464**, R = C_6H_4OMe-*p*) (58%), 2-(pyridin-4-yl)quinoxaline 1,4-dioxide (**464**, R = pyridin-4-yl) (35%), and other such quinoxalines were made similarly.[1035]

The same substrate (**462**) and vinyl acetate gave quinoxaline 1,4-dioxide (**465**) (Et_2NH, AcOEt, 0°C, 3 h, then 20°C, 72 h: 79%).[200,1012]

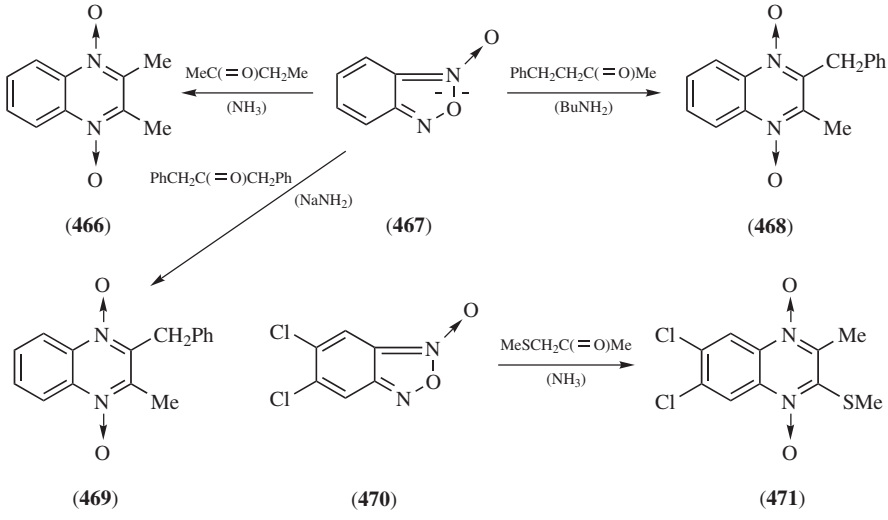
Also other examples.[166]

Simple Ketones as Synthons

Note: This subcategory includes the use of ketones such as 2-butanone, acetylacetone, ethyl acetoacetate, and acetoacetonitrile.

2,1,3-Benzoxadiazole 1-oxide (**467**) gave 2,3-dimethylquinoxaline 1,4-dioxide (**466**) (AcEt, NH_3–MeOH, 40–50°C, 5 h: 90%; also many homologs similarly),[242,cf. 230,610] 2-benzyl-3-methylquinoxaline 1,4-dioxide (**468**) ($PhCH_2CH_2Ac$, $BuNH_2$, MeOH, 20°C, 12 h: 83%),[627,cf. 291] or 2-benzyl-3-phenylquinoxaline 1,4-dioxide (**469**) [$(PhCH_2)_2CO$, $NaNH_2$, Et_2O, ?°C, ? h: 52%].[627]

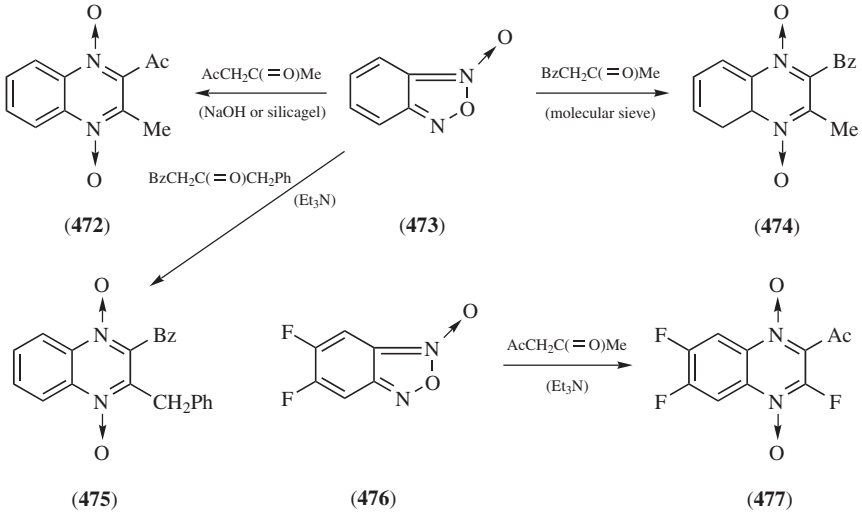
5,6-Dichloro-2,1,3-benzoxadiazole 1-oxide (**470**) and α-(methylthio)acetone gave 6,7-dichloro-2-methyl-3-methylthioquinoxaline 1,4-dioxide (**471**) (NH_3–MeOH, 20°C, 12 h: 30%);[483] many analogs likewise.[1086]



2,1,3-Benzoxadiazole 1-oxide (**473**) gave 2-acetyl-3-methylquinoxaline 1,4-dioxide (**472**) (Ac_2CH_2, NaOH, EtOH, 55°C, 90 min, then 20°C, 12 h: 54%;[153] or Ac_2CH_2 on SiO_2 gel, 20°C, 7 days: 58%),[991] 2-benzoyl-3-methylquinoxaline 1,4-dioxide (**474**) ($BzCH_2Ac$ on 3Å molecular sieve,

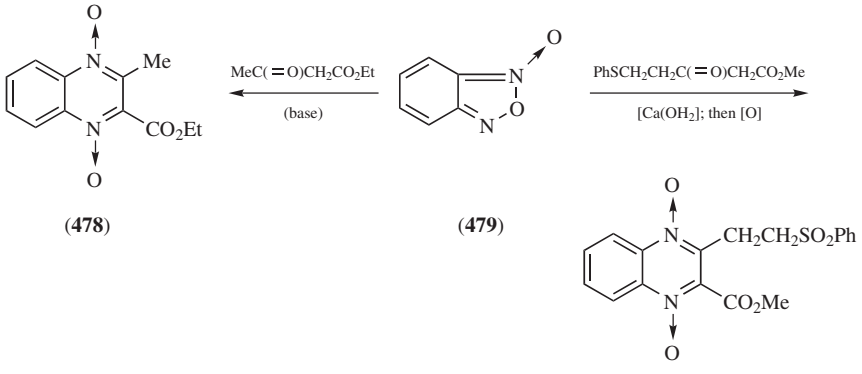
20°C, 2 days: 87%),[454] or 2-benzoyl-3-benzylquinoxaline, 1,4-dioxide (**475**) [$BzCH_2C(=O)CH_2Ph$, neat Et_3N, 20°C, 24 h: 21%).[627]

5,6-Difluoro-2,1,3-benzoxadiazole 1-oxide (**476**) gave 2-acetyl-6,7-difluoro-3-methylquinoxaline 1,4-dioxide (**477**) (Ac_2CH_2, neat Et_3N, 5°C, 1 h, then 20°C, 1 h: 72%; analogs likewise).[801,cf. 869,976]



(**472**) (**473**) (**474**) (**475**) (**476**) (**477**)

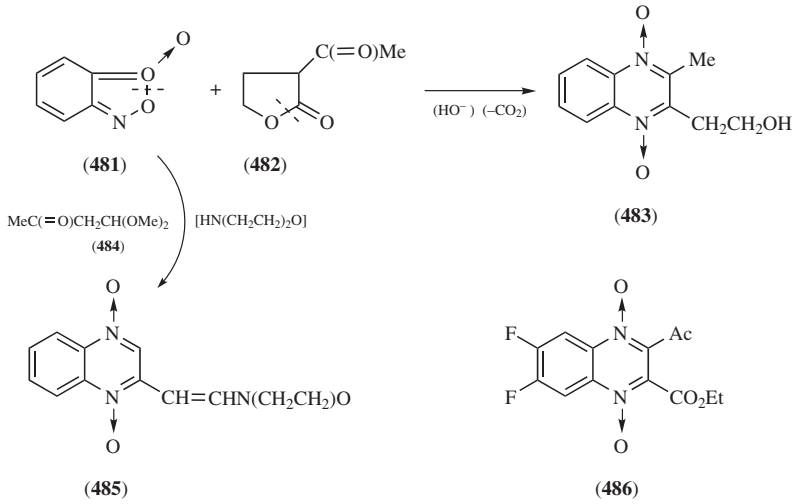
2,1,3-Benzoxadiazole 1-oxide (**479**) gave ethyl 3-methyl-2-quinoxalinecarboxylate 1,4-dioxide (**478**) [$AcCH_2CO_2Et$, neat $O(CH_2CH_2)_2NH$, 5°C→20°C, 10 h: ~85%;[226,883] NaOH, MeOH, 30°C→17°C, 30 h: 66% (structure confirmed by X-ray analysis),[925] or $H_2NCH_2CH_2OH$, MeOH, 50°C, light exclusion, 15 h: 41%][948] or methyl 3-(2-phenylthioethyl)-2-quinoxalinecarboxylate 1,4-dioxide, characterized as the corresponding 3-(2-phenylsulfonylethyl) derivatives (**480**) [$PhSCH_2CH_2C(=O)CH_2CO_2Me$, $Ca(OH)_2$, Pr^iOH-$CHCl_3$, 60°C, 2 h: then crude product, *m*-$ClC_6H_4CO_3H$, CH_2Cl_2, 20°C, 30 min: 40% overall].[710]



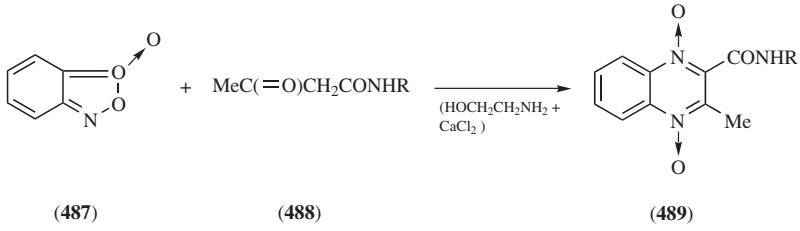
(**478**) (**479**) (**480**)

2,1,3-Benzoxadiazole 1-oxide (**481**) with 3-acetyltetrahydro-2-furanone (2-acetylbutyrolactone: **482**) gave 2-(2-hydroxyethyl)-3-methylquinoxaline 1,4-dioxide (**483**) (KOH, MeOH–H_2O, 20°C, 24 h: 50%)[244] but with 2-acetylacetaldehyde dimethyl acetal (**484**), in the presence of morpholine as base, it gave 2-(2-morpholinovinyl)quinoxaline 1,4-dioxide (**485**) (PhH, reflux, water separation, 9 h: 47%).[244]

5,6-Difluoro-2,1,3-benzoxadiazole 1-oxide and ethyl acetoacetate gave ethyl 6,7-difluoro-3-methyl-2-quinoxalinecarboxylate 1,4-dioxide (**486**) (neat Et_3N, <5°C, 1 h, then 20°C, 1 h: 60%);[907] analogs likewise.[801,907]



2,1,3-Benzoxadiazole 1-oxide (**487**) with 2-acetylacetamide (**488**, R = H) gave 3-methyl-2-quinoxalinecarboxamide 1,4-dioxide (**489**, R = H) ($HOCH_2CH_2NH_2$, $CaCl_2$, MeOH, 25–30°C, 12 h: 70%);[228] or with 2-acetylacetanilide (**488**, R = Ph) gave 3-methyl-*N*-phenyl-2-quinoxalinecarboxamide 1,4-dioxide (**489**, R = Ph) ($HOCH_2CH_2NH_2$, $CaCl_2$, MeOH, 25–30°, 10 h: 44%;[228] or 3Å molecular sieve, MeOH, 1 day: 88%).[454]

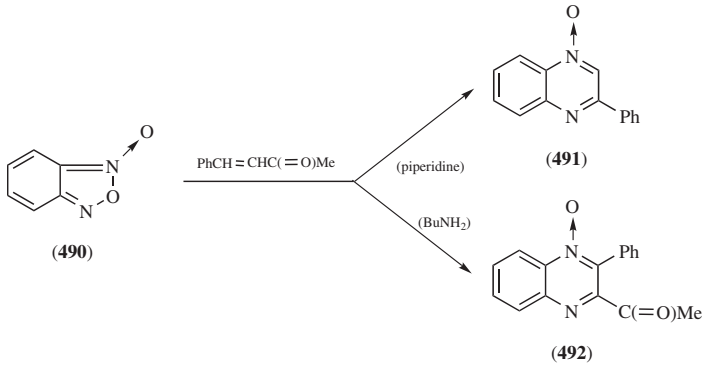


Also other examples.[137,166,182,540,616,706,804,991,1116]

α-Unsaturated ketones as Synthons

2,1,3-Benzoxadiazole 1-oxide (**490**) gave either 2-phenylquinoxaline 4-oxide (**491**) [PhCH=CHC(=O)Me, $HN(CH_2)_4$, MeCN, reflux, 24 h: 35%; note deacylation] or 2-acetyl-3-phenylquinoxaline 4-oxide (**492**) [PhCH +

CHC(=O)Me, $BuNH_2$, MeCN, reflux, 24 h: 16%; change in regioselectivity and preservation from deacylation may perhaps be explained by the possibility for Schiff base formation of the synthon and product, respectively, in the presence of the primary amine];[158] a plausible reason for the formation of mono- instead of di-*N*-oxides was advanced.[158]



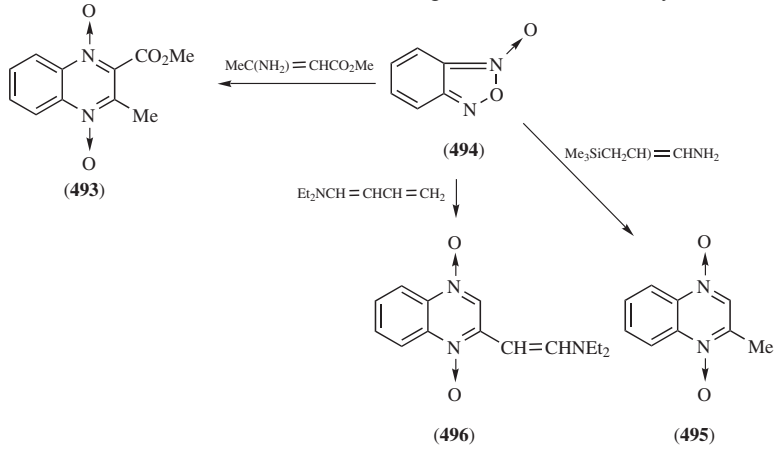
(**490**) (**491**) (**492**)

α-Enamines or α,γ-Dienamines as Synthons

Note: Such enamines usually react as alkenes but with deamination; the dienamines also react as alkenes but usually without deamination. No added base is needed for these reactions.

2,1,3-Benzoxadiazole 1-oxide (**494**) gave methyl 3-methyl-2-quinoxalinecarboxylate 1,4-dioxide (**493**) [$MeC(NH_2)=CHCO_2Me$, MeOH, reflux, 30 h: ~65%][587] or 2-methylquinoxaline 1,4-dioxide (**495**) ($Me_3SiCH_2CH=CHNH_2$, dioxane-MeOH, 50°C, 15 min, then reflux, 10 min: 41%; note desilylation as well as deamination).[219]

The same substrate (**494**) gave 2-(2-diethylaminovinyl)quinoxaline 1,4-dioxide (**496**) ($Et_2NCH=CHCH=CH_2$, Et_2O, 20°C, 4 h: 80%);[92,634] analogs with or without substituents in the benzene ring were made similarly.[634]

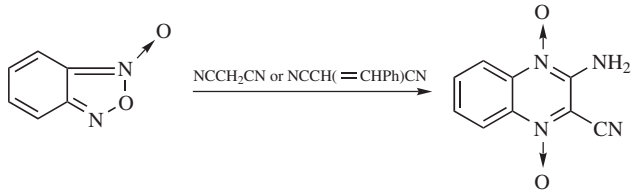


(**493**) (**494**) (**496**) (**495**)

Also other examples.[245,745]

Malononitriles as Synthons

2,1,3-Benzoxadiazole 1-oxide (**497**) and malononitrile gave 3-amino-2-quinoxalinecarbonitrile 1,4-dioxide (**498**) (Et_3N, Me_2NCHO, 25°, 90 min: 75%;[722] Et_3N, Me_2NCHO, 0°C→10°C, 4 h: 75%;[477] Et_3N, Me_2NCHO, 0°C→20°C, 24 h: 75%).[726] Symmetrically substituted substrates afforded products like 3-amino-6,7-dimethyl-2-quinoxalinecarbonitrile 1,4-dioxide (**499**), but unsymmetric substrates usually gave two isomeric products, such as 3-amino-6/7-trifluoromethyl-2-quinoxalinecarbonitrile 1,4-dioxide (**500**).[726]



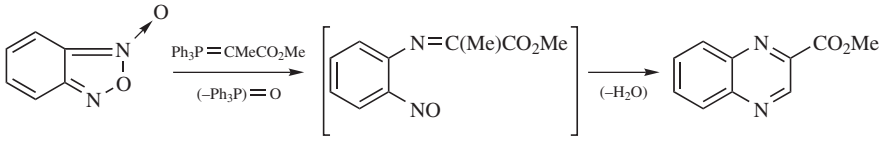
(**497**) (**498**)

(**499**) (**500**)

The substrate (**497**) and α-benzylidenemalononitrile [NCC(=CHPh)CN] also gave 3-amino-2-quinoxalinecarbonitrile 1,4-dioxide (**498**) (Et_3N, EtOH, 20°C, 4 h: 80%).[403]

Methyl 2-(Triphenylphosphoranylidene)propionate as a Synthon

2,1,3-Benzoxadiazole 1-oxide (**501**) and methyl 2-(triphenylphosphoranylidene)propionate gave several products from which methyl 2-quinoxalinecarboxylate (**503**), probably formed via the intermediate (**502**), was isolated (PhH, reflux, 6 h: 4%).[636]

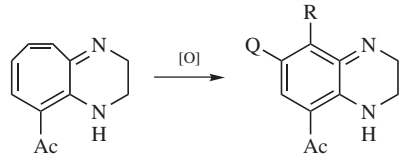


(**501**) (**502**) (**503**)

1.6.8. Cycloheptapyrazines as Substrates/Synthons

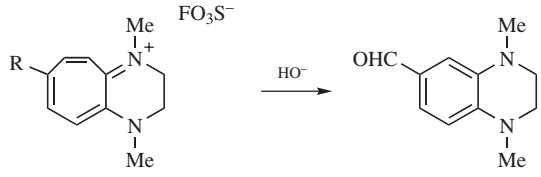
This synthesis has not been sufficiently developed to be of preparative value. Representative examples follow.

5-Acetyl-2,3-dihydro-4*H*-cycloheptapyrazine (**504**) gave a separable mixture of 8-acetyl-1,2,3,4-tetrahydro-5-quinoxalinecarbaldehyde (**505**, Q = H, R = CHO), the isomeric 6-quinoxalinecarbaldehyde (**505**, Q = CHO, R = H), and 5-acetyl-1,2,3,4-tetrahydroquinoxaline (**505**, Q = R = H) (H_2O_2, H_2O–MeOH, 20°C, 8 h: 3%, 2%, and 3%, respectively).[86]



(**504**) (**505**)

1,4-Dimethyl-2,3-dihydro-4*H*-cycloheptapyrazin-1-ium fluorosulfonate (**506**, R = H) or its derived 7-bromo derivative (**506**, R = Br) gave 1,4-dimethyl-1,2,3,4-tetrahydro-6-quinoxalinecarbaldehyde (**507**) (no details apart from characterization).[605]

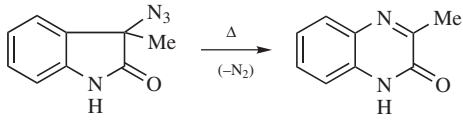


(**506**) (**507**)

1.6.9. Indoles as Substrates/Synthons

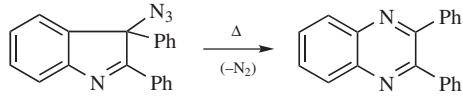
Two distinct routes from indoles to quinoxalines have been reported, but neither has been developed to any extent. Examples follow.

3-Azido-3-methyl-2-indolinone (**508**) gave 3-methyl-2(1*H*)-quinoxalinone (**509**) (xylene, reflux, 8 h: >95%).[586]



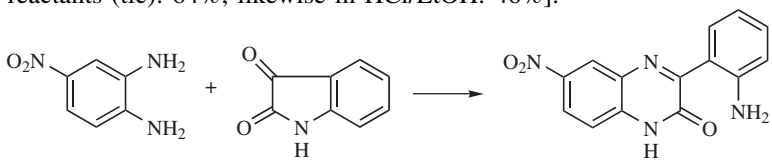
(**508**) (**509**)

3-Azido-2,3-diphenyl-3*H*-indole (**510**) gave mainly 2,3-diphenylquinoxaline (**511**) (Me_2NCHO, reflux, 16 h: 82%);[586,cf. 664] homologs and analogs made similarly.[586]



(**510**) (**511**)

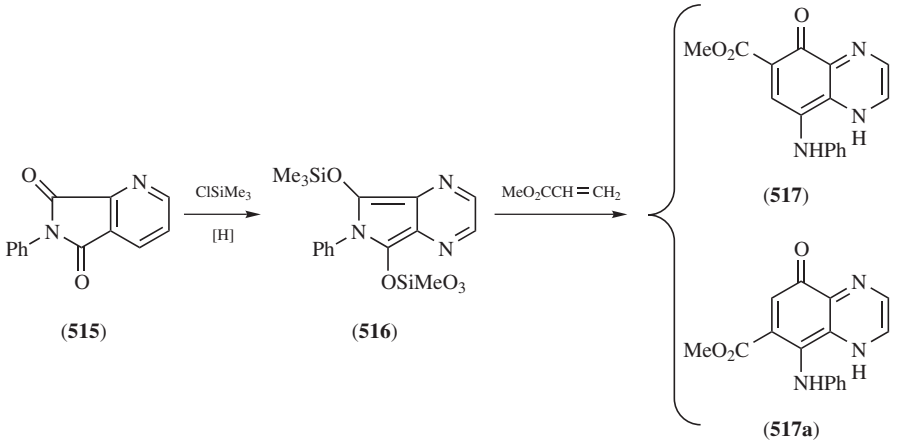
2,3-Indolinedione (isatin: **513**) and 4-nitro-1,2-benzenediamine (**512**) gave 3-*o*-aminophenyl-6-nitro-2(1*H*)-quinoxalinone (**514**) [AcOH, reflux until no reactants (tlc): 64%; likewise in HCl/EtOH: 46%].[774,cf. 770]



(**512**) (**513**) (**514**)

1.6.10. Pyrrolo[3,4-*b*]pyrazines as Substrates/Synthons

One interesting example of this type of synthesis has been reported. 6-Phenyl-5*H*-5,7(6*H*)-pyrrolo[3,4-*b*]pyrazine (**515**) underwent electrolytic reduction in the presence of chlorotrimethylsilane to give the (unisolated?) substrate (**516**) that reacted with methyl acrylate (minimal detail) to afford a mixture of methyl 8-anilino-5-oxo-1,5-dihydro-6-quinoxalinecarboxylate (**517**) and methyl 5-anilino-8-oxo-4,8-dihydro-6-quinoxalinecarboxylate (**517a**) (17% and 21%, respectively, after separation).[194]



(**515**) (**516**) (**517**) (**517a**)

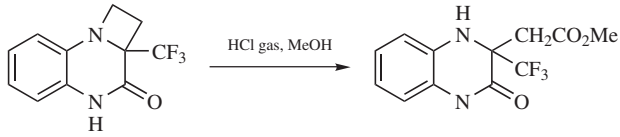
1.7. FROM HETEROPOLYCYCLIC SUBSTRATES/SYNTHONS

Many such substrates have been used for the primary synthesis of quinoxalines, but few such procedures are of general significance, although some have been decidedly useful in particular cases. Accordingly, the following subsections (arranged in alphabetical order according to the heterocyclic system involved) are each brief.

1.7.1. Azeto- or Azirino[1,2-*a*]quinoxalines as Substrates/Synthons

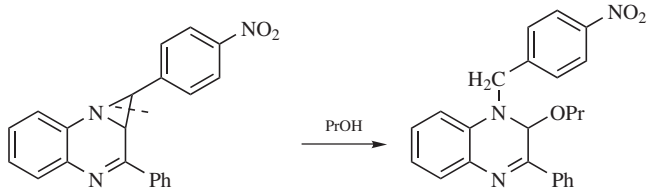
These syntheses are illustrated in the following examples.

2a-Trifluoromethyl-2,2a-dihydro-1*H*-azeto[1,2-*a*]quinoxaline-1,3(4*H*)-dione (**518**) gave 3-methoxycarbonylmethyl-3-trifluoromethyl-3,4-dihydro-2(1*H*)-quinoxalinone (**518a**) (HCl, MeOH, ''facile'').[595]



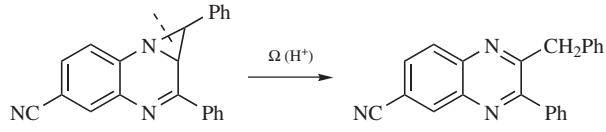
(**518**) (**518a**)

1-*p*-Nitrophenyl-2-phenyl-1,1a-dihydroazirino[1,2-*a*]quinoxaline (**519**) gave 1-*p*-nitrobenzyl-3-phenyl-2-propoxy-1,2-dihydroquinoxaline (**520**) by an addition mechanism (PrOH, reflux, 1 h: 58%).[771]



(**519**) (**520**)

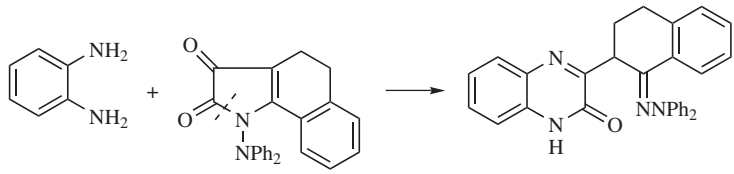
In contrast, 1,2-diphenyl-1,1a-dihydroazirino[1,2-*a*]quinoxaline-5-carbonitrile (**521**) gave 2-benzyl-3-phenyl-6-quinoxalinecarbonitrile (**522**) by rearrangement (HCl–H_2O–AcMe, reflux, ? h: 86%);[789] also analogs likewise.[789]



(**521**) (**522**)

1.7.2. Benz[*g*]indoles as Substrates/Synthons

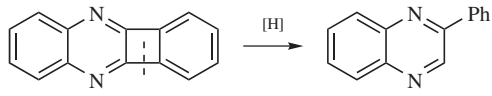
o-Phenylenediamine (**523**) reacted with 1-diphenylamino-2,3,4,5-tetrahydro-1*H*-benz[*g*]indole-2,3-dione (**524**) in dichloromethane (containing a trace of hydrogen chloride) during 48 h at 20°C to afford 3-(1-diphenylhydrazono-1,2,3,4-tetrahydronaphthalen-2-yl)-2(1*H*)-quinoxalinone (**525**) in 48% yield.[1002]



(**523**) (**524**) (**525**)

1.7.3. Benzo[3,4]cyclobuta[1,2-*b*]quinoxalines as Substrates/Synthons

Reduction of unsubstituted benzo[3,4]cyclobuta[1,2-*b*]quinoxaline (**526**) with Raney nickel in refluxing ethanol during 30 min gave 2-phenylquinoxaline (**527**) in 78% yield.[629]



(**526**) (**527**)

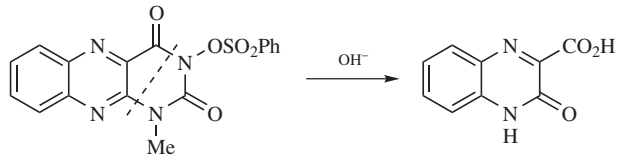
1.7.4. Benzo[*g*]pteridines as Substrates/Synthons (*E* 140)

Just as 2- or 4-substituted pteridines are usually degraded to pyrazines,[1055] similarly substituted benzo[*g*]pteridines have also been observed to afford quinoxalines under vigorous hydrolytic or aminolytic conditions. The following examples illustrate some such degradations.

7,8-Dichlorobenzo[*g*]pteridine-2,4(1*H*,3*H*)-dione (7,8-dichloroalloxazine: **528**) gave 6,7-dichloro-2-quinoxalinamine (**529**) (neat H_2SO_4, 240°C, 10 min: 48%).[1044]

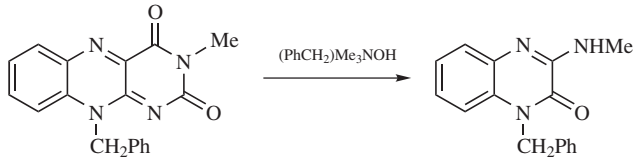
(**528**) (**529**)

3-Benzenesulfonyloxy-1-methylbenzo[*g*]pteridine-2,4(1*H*,3*H*)-dione (**530**) gave 3-oxo-3,4-dihydro-2-quinoxalinecarboxylic acid (**531**) (1.3M NaOH, 90°C, 5 min: 40–48%).[384,456]



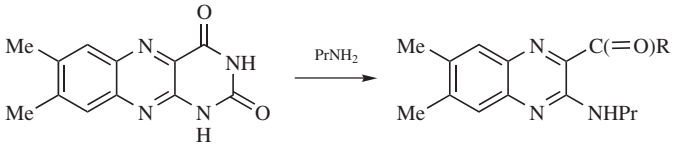
(**530**) (**531**)

10-Benzyl-3-methylbenzo[*g*]pteridine-2,4(3*H*,10*H*)-dione (**532**) gave, among other products, 1-benzyl-3-methylamino-2(1*H*)-quinoxalinone (**533**) [Me-($PhCH_2$)NOH, Me_2NCHO, 20°C, light exclusion, 9 h: 15% after separation; mechanism obscure].[535]



(**532**) (**533**)

7,8-Dimethylbenzo[*g*]pteridine-2,4(1*H*,3*H*)-dione (**534**) gave a separable mixture of 2-allophanoyl-6,7-dimethyl-3-propylaminoquinoxaline (**535a**), 6,7-dimethyl-2-(*N*′-propylallophanoyl)-3-propylaminoquinoxaline (**535b**), 6,7-dimethyl-3-propylamino-2-quinoxalinecarboxamide (**535c**), 6,7-dimethyl-3-propylamino-2-quinoxalinecarboxylic acid (**535d**), and 6,7-dimethyl-*N*-propyl-3-propylamino-2-quinoxalinecarboxamide (**535e**) (neat $PrNH_2$, 60°C, sealed, 1 h: 10%, 20%, 14%, 22%, and 3%, respectively);[466] other alkylamines gave homologous products;[466] and the monothio substrate, 7,8-dimethyl-4-thioxo-3,4-dihydrobenzo[*g*]pteridin-2(1*H*)-one, afforded a similar range of products with alkylamines.[466]

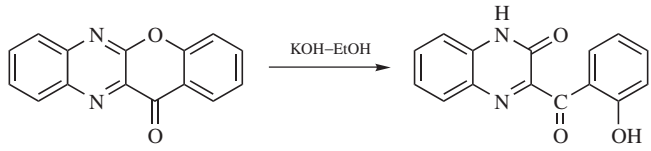


(**534**) (**535**)

(**a**) R = $NHCONH_2$
(**b**) R = NHCONHPr
(**c**) R = NH_2
(**d**) R = OH
(**e**) R = NHPr

1.7.5. [1]Benzopyrano[2,3-*b*]quinoxalines as Substrates/Synthons

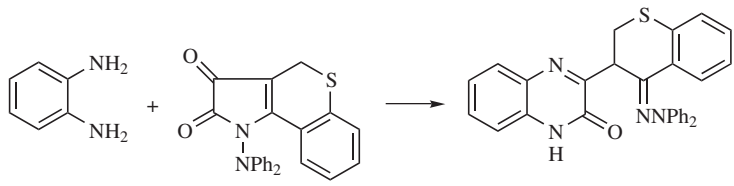
12*H*-[1]Benzopyrano[2,3-*b*]quinoxalin-12-one (**536**) underwent pyrolytic fission in refluxing ethanolic alkali during 4 h to afford 3-*o*-hydroxybenzoyl-2(1*H*)-quinoxalinone (**537**) in 84% yield.[233]



(**536**) (**537**)

1.7.6. [1]Benzothiopyrano[4,3-*b*]pyrroles as Substrates/Synthons

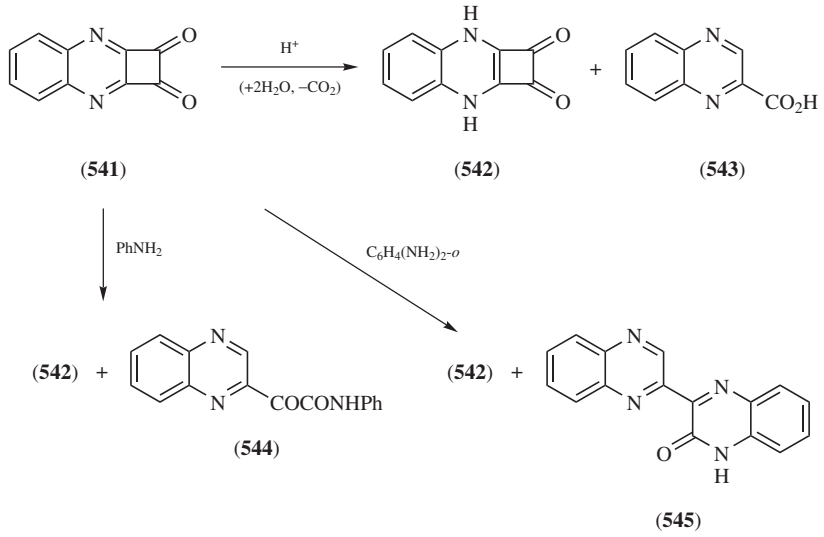
1,2-Benzenediamine (**538**) and 1-diphenylamino-3,4-dihydro-[1]benzothiopyrano[4,3-*b*]pyrrole-2,3(1*H*)-dione (**539**) in dichloromethane (containing a trace of hydrogen chloride) at 20°C for 48 h furnished 3-(4-diphenylhydrazono-3,4-dihydro-2*H*-[1]benzothiopyran-3-yl)-2(1*H*)-quinoxalinone (**540**) in 30% yield.[1002]



(**538**) (**539**) (**540**)

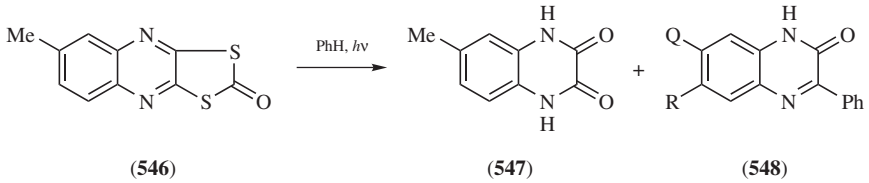
1.7.7. Cyclobuta[*b*]quinoxalines as Substrates/Synthons

1,2-Dihydrocyclobuta[*b*]quinoxaline-1,2-dione (**541**) (2 equiv) reacted rapidly with water (in boiling 2M HCl) to give 1,2,3,8-tetrahydrocyclobuta[*b*]quinoxaline-1,2-dione (**542**) and 2-quinoxalinecarboxylic acid (**543**) (in 50% and 43% yields, respectively, after separation), presumably with loss of CO_2.[309] The same substrate (**541**) with ethanolic aniline (at 20°C until the green color faded) gave the reduced product (**542**) and 2-(*N*-phenyloxamoyl)quinoxaline (**544**) (11% and 57% yields, respectively, after separation); or with 1,2-benzenediamine (in boiling glycol for ~3 min) gave the same reduced product (**542**) and 2,2′-biquinoxalin-3(4*H*)-one (**545**) (63%).[309]



1.7.8. 1,3-Dithiolo[4,5-*b*]quinoxalines as Substrates/Synthons

It has been observed that photolysis of the fungicide, 6-methyldithiolo[4,5-*b*]-quinoxalin-2-one (quinomethionate: **546**) in benzene during 8 h afforded not only 6-methyl-2,3(1*H*,4*H*)-quinoxalinedione (**547**) but also the isomeric phenylated products, 6-methyl- (**548**, Q = H, R = Me) and 7-methyl-3-phenyl-2(1*H*)-quinoxalinone (**548**, Q = Me, R = H).[325]

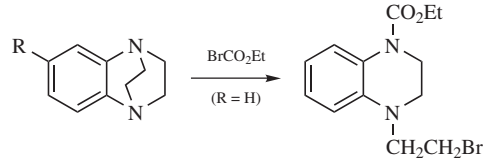


1.7.9. 1,4-Ethanoquinoxalines as Substrates/Synthons

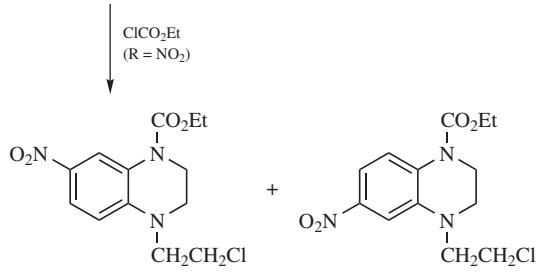
The ethano bridge in some 1,4-ethanoquinoxalines may be displaced from one ring nitrogen to furnish *N*-(substituted ethyl) hydroquinoxalines. Several aspects of this fundamental reaction are illustrated in the following examples.

2,3-Dihydro-1,4-ethanoquinoxaline (**549**, R = H) and ethyl bromoformate (prepared in situ) gave ethyl 4-(2-bromoethyl)-1,2,3,4-tetrahydro-1-quinoxalinecarboxylate (**550**, R = H) (MeCN, −40°C→20°C, 2 h: 33%).[792]

The unsymmetric 6-nitro-2,3-dihydro-1,4-ethanoquinoxaline (**549**, $R = NO_2$) and ethyl chloroformate naturally gave a mixture of ethyl 4-(2-chloroethyl)-7-nitro- (**551**) and ethyl 4-(2-chloroethyl)-6-nitro-1,2,3,4-tetrahydro-1-quinoxalinecarboxylate (**552**) ($CHCl_3$, 20°C, 1 h: ~30% each, after separation.[791]

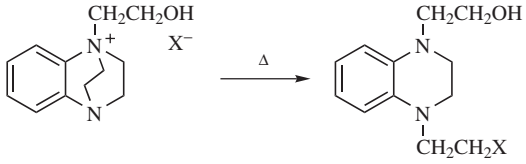


(**549**) (**550**)



(**551**) (**552**)

Each quaternary 1-(2-hydroxyethyl)-2,3-dihydro-1,4-ethanoquinoxalin-1-ium halide (**553**, X = Cl, Br, or I) underwent thermolysis to give the corresponding 1-(2-halogenoethyl)-4-(2-hydroxyethyl)-1,2,3,4-tetrahydroquinoxaline (**554**, X = Cl, Br, or I) (PhMe, reflux, 4 h: >70%);[798] also other such transformations.[392,798]

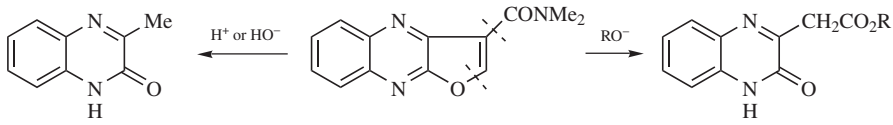


(**553**) (**554**)

1.7.10. Furo[2,3-*b*]quinoxalines as Substrates/Synthons

N,*N*-Dimethylfuro[2,3-*b*]quinoxaline-3-carboxamide (**556**) (as hydrochloride) in hot acidic or alkaline media for 1 h gave 3-methyl-2(1*H*)-quinoxalinone (**555**) in 60% or 95% yield, respectively;[342,588] In contrast, the same amidic substrate (**556**) in hot alcoholic alkoxide afforded 3-ethoxycarbonylmethyl- (**557**, R = Et) or

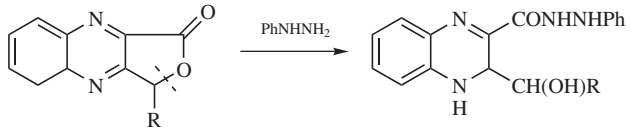
3-methoxycarbonylmethyl-2(1*H*)-quinoxalinone (**557**, R = Me) in 80% or 57% yield, respectively, according to the alcohol employed.[542,588]



(**555**) (**556**) (**557**)

1.7.11. Furo[3,4-*b*]quinoxalines as Substrates/Synthons

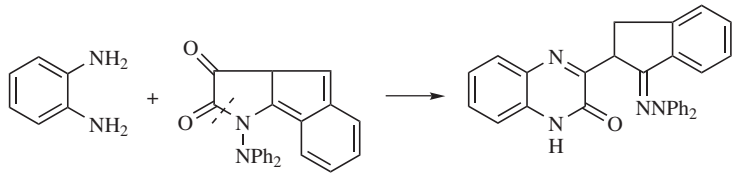
3-Methyl-1,3-dihydrofuro[3,4,-*b*]quinoxalin-1-one (**558**, R = Me) reacted with phenylhydrazine in refluxing methanolic solution during 16 h to give 3-(1-hydroxyethyl)-*N*′-phenyl-2-quinoxalinecarbohydrazide (**559**, R = Me) in 75% yield;[259] 3-(1,2-dihydroxyethyl)-1,3-dihydrofuro[3,4-*b*]quinoxalin-1-one (**558**, R = CHOH-CH_2OH) likewise afforded *N*′-phenyl-3-(1,2,3-trihydroxypropyl)-2-quinoxalinecarbohydrazide (**559**, R = $CHOHCHOHCH_2OH$);[914] and several *N*′-(substituted phenyl) analogs were made similarly.[914] Also related examples.[1097]



(**558**) (**559**)

1.7.12. Indeno[1,2-*b*]pyrroles as Substrates/Synthons

1,2-Benzenediamine (**560**) and 1-diphenylamino-1,2,3,4-tetrahydroindeno[1,2-*b*]pyrrole (**561**) in dichloromethane containing a trace of hydrogen chloride at 20°C during 48 h afforded 3-(1-diphenylhydrazono-2,3-dihydro-1*H*-inden-2-yl)-2(1*H*)-quinoxalinone (**562**) in 53% yield.[1002]

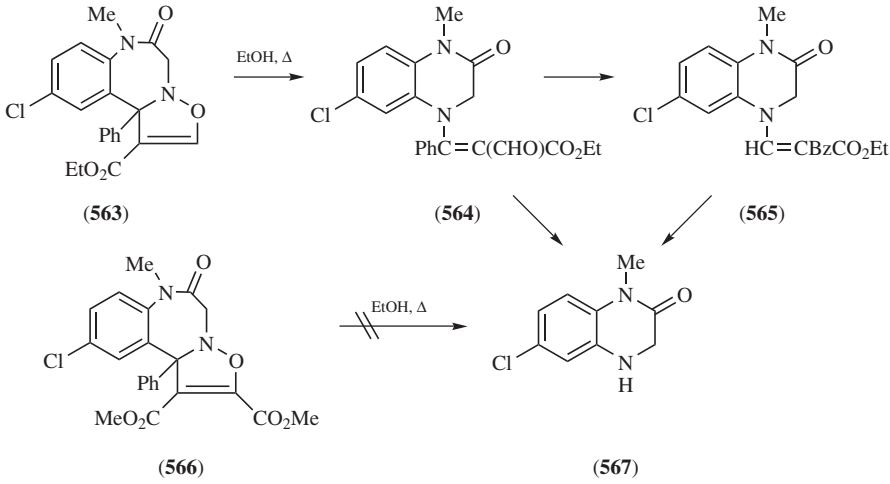


(**560**) (**561**) (**562**)

1.7.13. Isoxazolo[2,3-*d*][1,4]benzodiazepines as Substrates/Synthons

Several interesting quinoxalines can be obtained by this synthesis, as illustrated in the following examples.

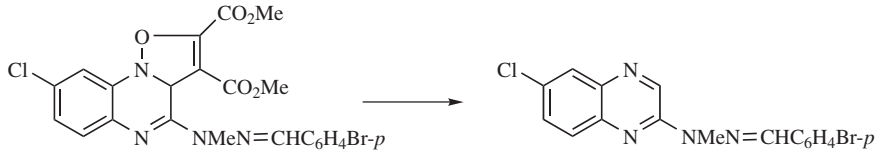
Ethyl 10-chloro-7-methyl-6-oxo-11b-phenyl-5,6,7,11b-tetrahydroisoxazolo[2,3-*d*][1,4]benzodiazepine-1-carboxylate (**563**) gave a separable mixture of 6-chloro-4-(2-ethoxycarbonyl-2-formyl-1-phenylvinyl)-1-methyl-3,4-dihydro-2(1*H*)-quinoxalinone (**564**), 4-(2-benzoyl-2-ethoxycarbonylvinyl)-6-chloro-1-methyl-3,4-dihydro-2(1*H*)-quinoxalinone (**565**), and 6-chloro-1-methyl-3,4-dihydro-2(1*H*)-quinoxalinone (**567**) (EtOH, reflux, 21 h: ~2%, ~8%, and ~20%, respectively, after separation; structures **564** and **565** were checked by X-ray analysis).[106]



An analogous substrate, dimethyl 10-chloro-7-methyl-6-oxo-11b-phenyl-5,6,7,11b-tetrahydroisoxazolo[2,3-d][1,4]benzodiazepine-1,2-dicarboxylate (**566**), gave not **567** but 6-chloro-1-methyl-2(1*H*)-quinoxalinone (EtOH, reflux, 30 h: ~40%).[585]

1.7.14. Isoxazolo[2,3-*a*]quinoxalines as Substrates/Synthons

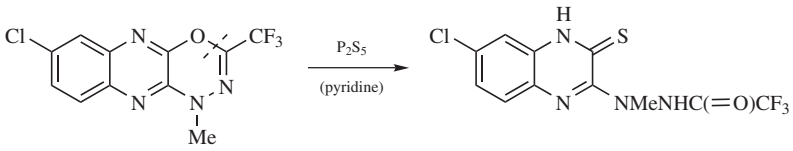
Dimethyl 4-(*N*′-*p*-bromobenzylidene-*N*-methylhydrazino)-8-chloro-3a*H*-isoxazolo[2,3-*a*]quinoxaline-2,3-dicarboxylate (**568**) in refluxing dimethylformamide for 10 h afforded 2-(*N*′-*p*-bromobenzylidene-*N*-methylhydrazino)-6-chloroquinoxaline (**569**) in 17% yield.[472]



(**568**) (**569**)

1.7.15. [1,3,4]Oxadiazino[5,6,*b*]quinoxalines as Substrates/Synthons

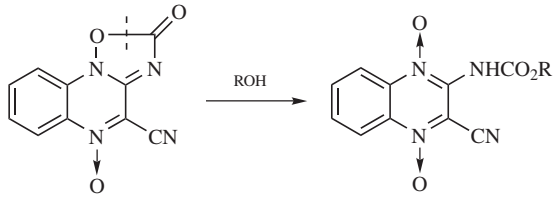
7-Chloro-1-methyl-3-trifluoromethyl-1*H*-[1,3,4]oxadiazino[5,6-*b*]quinoxaline (**570**) suffered thiolytic ring fission in refluxing pyridine (containing phosphorus pentasulfide) during 1 h to provide 7-chloro-3-[*N*-methyl-*N*′-(trifluoroacetyl)hydrazino]-2(1*H*)-quinoxalinethione (**571**) in 87% yield.[496]



(**570**) (**571**)

1.7.16. [1,2,4]Oxadiazolo[2,3-*a*]quinoxalines as Substrates/Synthons

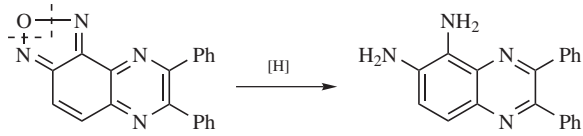
Several of these oxadiazoloquinoxaline 5-oxides have been converted into quinoxaline 1,4-dioxides. For example, 2-oxo-2*H*-[1,2,4]oxadiazolo[2,3-*a*]quinoxaline-4-carbonitrile 5-oxide (**572**) in refluxing ethanol or 2-propanol for ~2 h gave 3-ethoxycarbonylamino- (**573**, R = Et) or 3-isopropoxycarbonylamino-2-quinoxalinecarbonitrile 1,4-dioxide (**573**, R = Pr^i) in 61% or 74% yield, respectively;[490] 10 other analogous products with 6- and/or 7-substituents were made unambiguously in a similar way.[490]



(**572**) (**573**)

1.7.17. [1,2,5]Oxadiazolo[3,4-*f*]quinoxalines as Substrates/Synthons

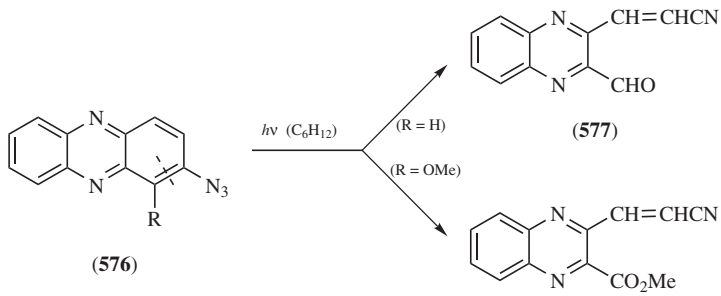
Reduction of 7,8-diphenyl[1,2,5]oxadiazolo[3,4-*f*]quinoxaline (**574**) with sodium bis(2-methoxyethoxy) aluminum hydride in refluxing toluene for 1 h gave 2,3-diphenyl-5,6-quinoxalinediamine (**575**) in 64% yield.[632]



(**574**) (**575**)

1.7.18. Phenazines as Substrates/Synthons

Photolysis of several 2-azidophenazines has been shown to afford quinoxalines. Thus irradiation of 2-azidophenazine (**576**, R = H) in cyclohexane or acetonitrile gave, among other products, 3-(2-cyanovinyl)-2-quinoxalinecarbaldehyde (**577**) in $\leq$17% yield;[113,987] and irradiation of 2-azido-1-methoxyphenazine in degassed benzene or acetonitrile gave, among other products, a separable mixture of *cis*- and *trans*-isomers of methyl 3-(2-cyanovinyl)-2-quinoxalinecarboxylate (**578**), each in low yield.[113,986]

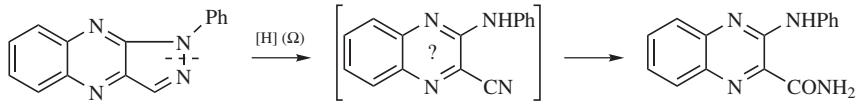


(**576**) (**577**) (**578**)

1.7.19. Pyrazolo[3,4-*b*]quinoxalines as Substrates/Synthons

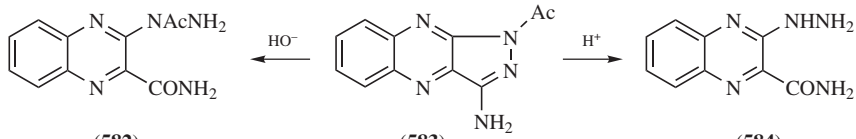
Pyrazolo[3,4-*b*]quinoxalines can undergo ring fission under reductive or hydrolytic conditions to give different types of quinoxaline. The following examples illustrate these possibilities.

1-Phenyl-1*H*-pyrazolo[3,4-*b*]quinoxaline (**579**) gave 3-anilino-2-quinoxalinecarboxamide (**581**) [$NaBH_4$, Pr^iOH, reflux, 80 h: 58%; the proposed mechanism via the nitrile (**580**) is unconvincing, but the fact remains];[430] the analogous 3-*p*-chloroanilino-2-quinoxalinecarboxamide was made similarly in 30% yield.[440]



(**579**) (**580**) (**581**)

1-Acetyl-1*H*-pyrazolo[3,4-*b*]quinoxalin-2-amine (**583**) gave either 3-(*N*-acetylhydrazino)- (**582**) (Na_2CO_3, MeOH, reflux, 20 h: 65%) or 3-hydrazino-2-quinoxalinecarboxamide (**584**) (2M HCl, 95°C, 1 h: 70%).[448]



(**582**) (**583**) (**584**)

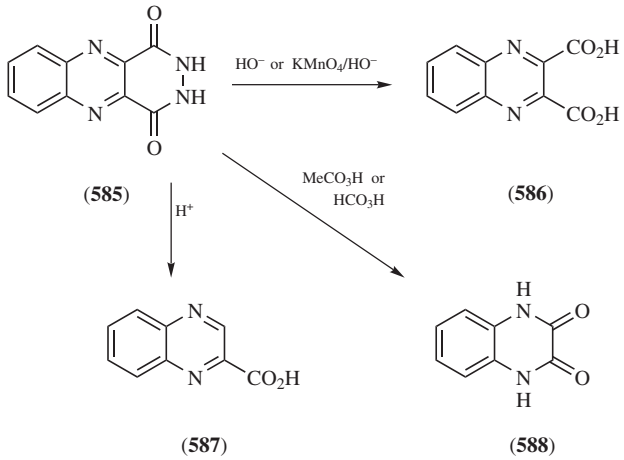
1.7.20. Pyridazino[4,5,-*b*]-quinoxalines as Substrates/Synthons

These pyridazinoquinoxalines can give different quinoxalines by hydrolytic or oxidative degradation. The potential for this route is illustrated in the few reported examples that follow.

Pyridazino[4,5-*b*]-quinoxaline-1,4(2*H*,3*H*)-dione (**585**) gave 2,3-quinoxalinedicarboxylic acid (**586**) (2M NaOH, reflux, 6 h: 87%; $KMnO_4$, NaOH, H_2O, reflux, 4 h: 34%; $KMnO_4$, AcMe, $CO_2\downarrow$, 20°C, 7 h: 70%).[751]

The same substrate (**585**) gave 2-quinoxalinecarboxylic acid (**587**) (2M HCl, reflux, 50 h: 98%; 96% H_2SO_4, 90°C, 15 h: 94%).[751]

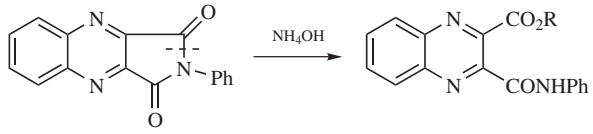
The same substrate (**585**) gave 2,3(1*H*,4*H*)-quinoxalinedione (**588**) (30% H_2O_2, AcOH, 70°C, 20 h: 62%; 30% H_2O_2, 85% HCO_2H, 60°C, 15 h: 59%).[751]



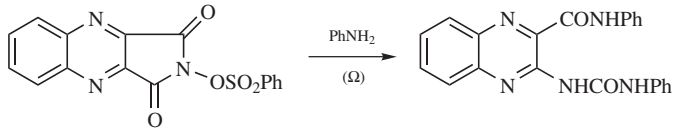
1.7.21. Pyrrolo[3,4-*b*]quinoxalines as Substrates/Synthons

The conversion of this system into quinoxalines is confined at present to the ring opening of *N*-substituted-2,3-quinoxalinedicarboximides, as illustrated in the following examples.

2-Phenyl-1*H*-pyrrolo[3,4-*b*]quinoxaline-1,3(2*H*)-dione (**589**) gave 3-(*N*-phenylcarbamoyl)-2-quinoxalinecarboxylic acid (**590**, R = H) initially as the crude ammonium salt (**590**, R = NH_4) (NH_3, H_2O, reflux, 4 h: ?%).[633]

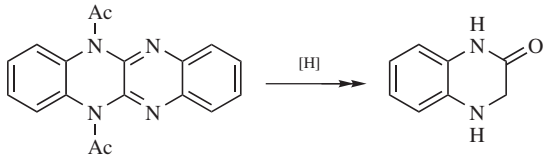


2-Benzenesulfonyloxy-1*H*-pyrrolo[3,4-*b*]quinoxaline-1,3(2*H*)-dione (**591**) gave *N*-phenyl-3-(*N*′-phenylureido)-2-quinoxalinecarboxamide (**592**) ($PhNH_2$, PhH, 20°C, 6 h: 82%; the mechanism probably involved Lossen rearrangement at an intermediate stage but remains unprove);[623] *N*-*p*-tolyl-3-(*N*′-*p*-tolylureido)-2-quinoxalinecarboxamide (87%) was made similarly using *p*-toluidine.[623]



1.7.22. Quinoxalino[2,3-*b*]quinoxalines as Substrates/Synthons

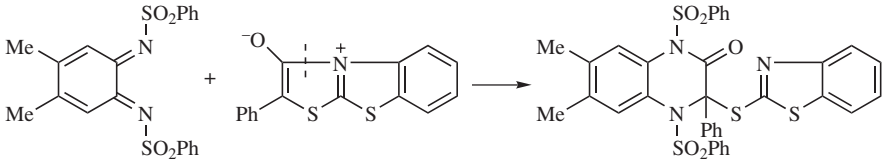
Electrolytic reduction of 5,12-diacetyl-5,12-dihydroquinoxalino[2,3-*b*]quinoxaline (**593**) in H_2SO_4–H_2O–MeOH afforded 3,4-dihydro-2(1*H*)-quinoxalinone (**594**) in unstated yield; a mechanism was suggested.[79]



(**593**) (**594**)

1.7.23. Thiazolo[2,3-*b*]benzothiazoliums as Substrates/Synthons

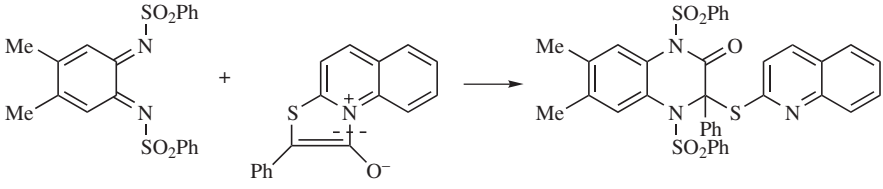
1,2-Bis(benzenesulfonylimino)-4,5-dimethylbenzene (**595**) reacted rapidly with 2-phenylthiazolo[2,3-*b*]benzothiazolium-3-olate (**596**) in dichloromethane at 20°C to give 1,4-bis(benzenesulfonyl)-3-(benzothiazol-2-ylthio)-6,7-dimethyl-3-phenyl-3,4-dihydro-2(1*H*)-quinoxalinone (**597**) in 95% yield.[964]



(**595**) (**596**) (**597**)

1.7.24. Thiazolo[3,2-*a*]quinoliniums as Substrates/Synthons

As in the preceding subsection, 1,2-bis(benzenesulfonylimino)-4,5-dimethylbenzene (**598**) and 2-phenylthiazolo[3,2-*a*]quinolinium-1-olate (**599**) in dichloromethane at 20°C during 15 min afforded 1,4-bis(benzenesulfonyl)-6,7-dimethyl-3-phenyl-3-(quinolin-2-ylthio)-3,4-dihydro-2(1*H*)-quinoxalinone (**600**) in almost quantitative yield.[964]

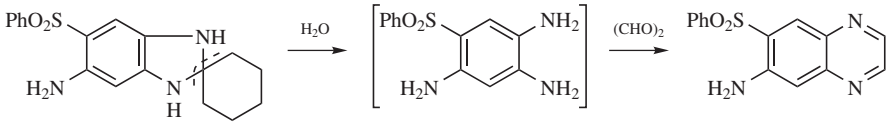


(**598**) (**599**) (**600**)

1.8. FROM SPIRO HETEROCYCLIC SUBSTRATES

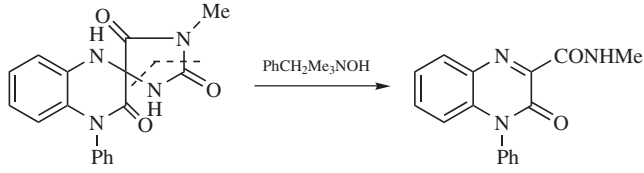
A few miscellaneous spiro heterocyclic compounds have been shown to act as substrates for the primary synthesis of regular quinoxalines. However, none of the following recent examples appears to have much potential as a preparative method.

6-Phenylsulfonyl-1,3-dihydrospiro[2*H*-benzimidazole-2,1′-cyclohexan]-5-amine (**601**) gave 7-phenylsulfonyl-6-quinoxalinamine (**602**) [MeOH–H_2O, 60°C, 20 min; then $(CHO)_2$–$NaHSO_2$↓, 95°C, 5 min: 55%; clearly a two-stage one-pot synthesis via the unisolated intermediate shown];[538] 7-morpholino-6-quinoxalinamine was obtained (57%) by a similar reaction.[538]



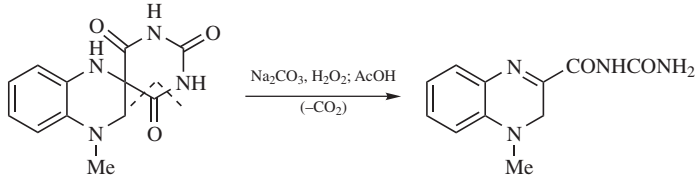
(**601**) (**602**)

1-Methyl-4′-phenylspiro[imidazolidine-4,2′(1′*H*)-quinoxaline]-2,3′,5(4′*H*)-trione (**603**) gave *N*-methyl-3-oxo-4-phenyl-3,4-dihydro-2-quinoxalinecarboxamide (**604**) ($PhMe_3NOH$, Me_2NCHO, dark, 125°C, 1 h: 66%, after separation from a byproduct).[535,672]



(**603**) (**604**)

4′-Methyl-3′-,4′-dihydrospiro[pyrimidine-5(2*H*),2′(1′*H*)-quinoxaline]-2,4,6(1*H*,3*H*)-trione (**605**) gave 1-methyl-3-ureidocarbonyl-1,2-dihydroquinoxaline (**606**) (2M Na_2CO_3, 15% H_2O_2, then AcOH↓: 74%; two homologs similarly; mechanism discussed).[619]

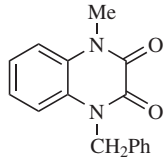
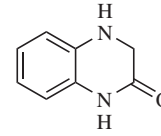
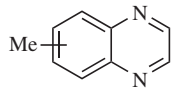
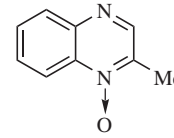
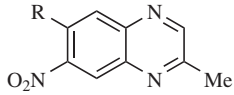
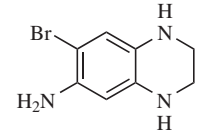
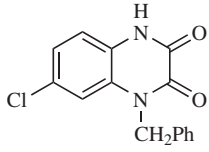
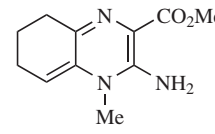
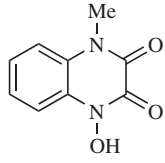
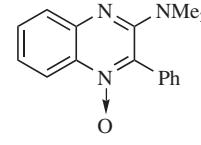


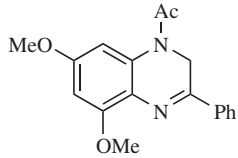
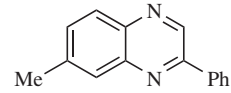
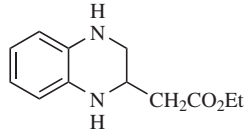
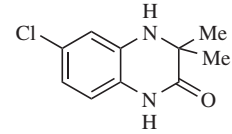
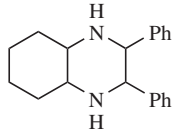
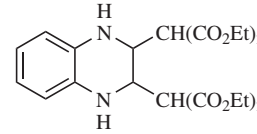
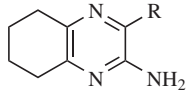
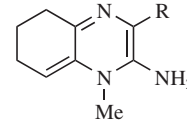
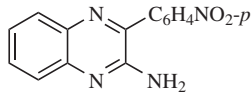
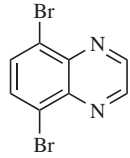
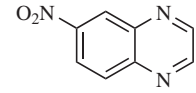
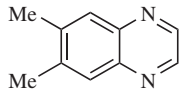
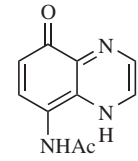
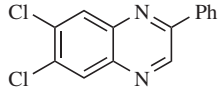
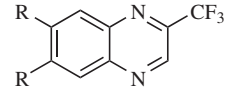
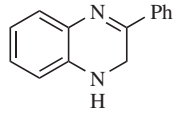
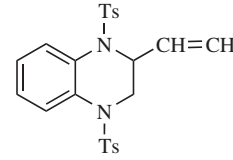
(**605**) (**606**)

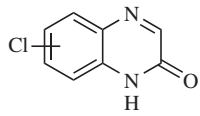
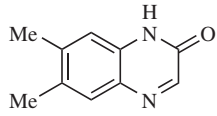
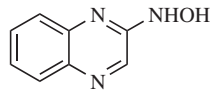
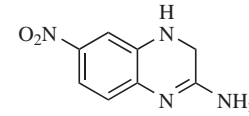
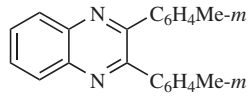
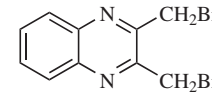
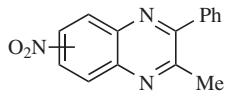
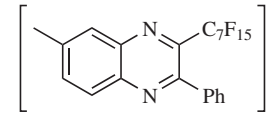
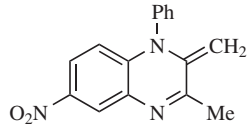
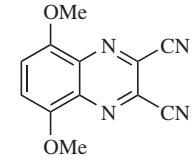
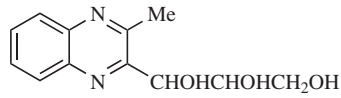
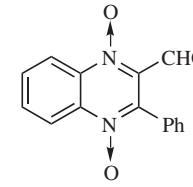
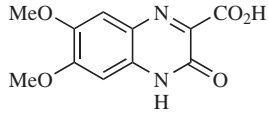
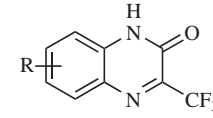
1.9. GLANCE INDEX TO TYPICAL QUINOXALINE DERIVATIVES AVAILABLE BY PRIMARY SYNTHESES

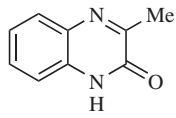
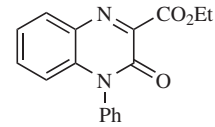
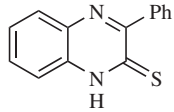
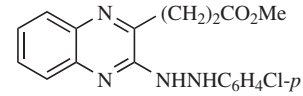
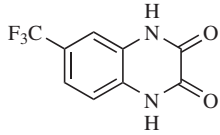
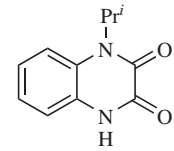
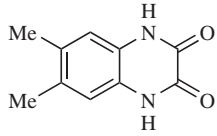
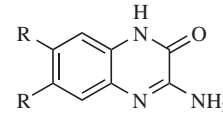
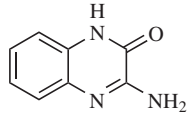
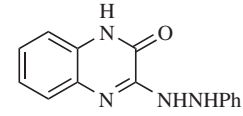
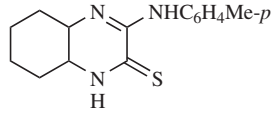
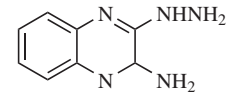
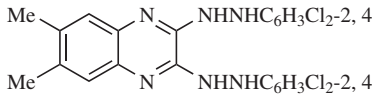
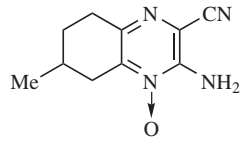
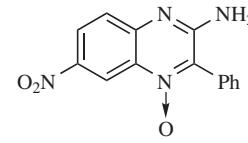
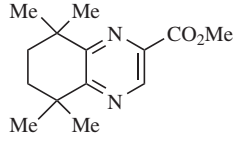
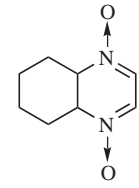
This glance index may assist in the choice of a primary synthesis to provide a required type of quinoxaline derivative. In using the index, it should be borne in mind that products broadly analogous to those formulated may often be obtained by minor modification(s) to the substrate or synthon employed: for example, by change, addition, or deletion of alkyl or aryl groups; by interchange of halogeno substituents; by modification or interchange of acid, ester, amide, or similar groupings; by interchange of oxo, thioxo, selenoxo, or imino substituents; by interchange of alkoxy, aryloxy, or alkylthio groups; and so on.

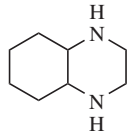
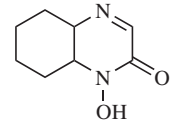
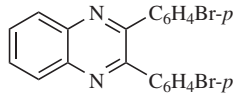
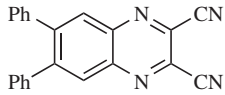
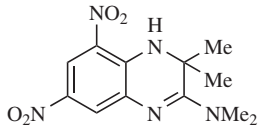
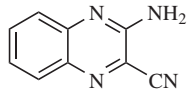
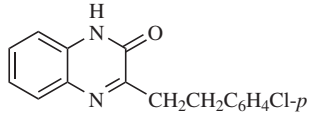
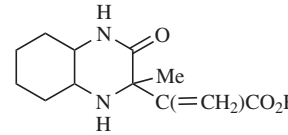
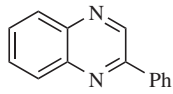
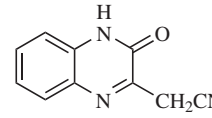
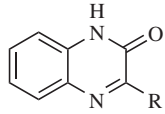
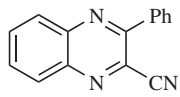
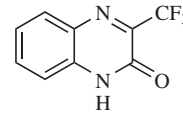
Procedures that afford very poor yields or employ substrates or synthons difficult to access are usually omitted; so, too, are syntheses that appear to lack general applicability in their present state of development, although they may well prove useful eventually.

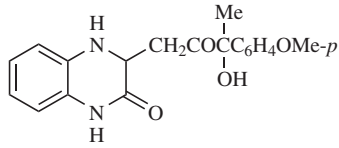
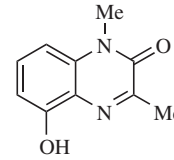
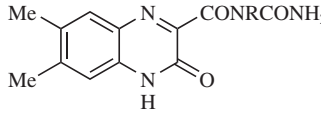
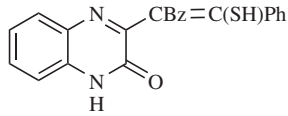
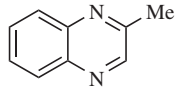
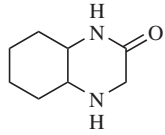
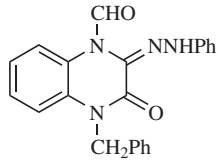
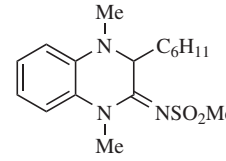
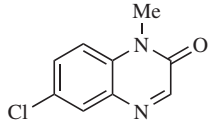
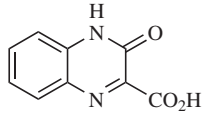
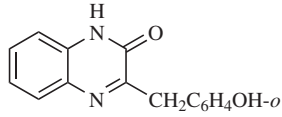
Section	Typical Products	
1.1.1		
		
1.1.2.1		
		
1.1.2.2		

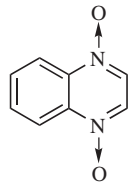
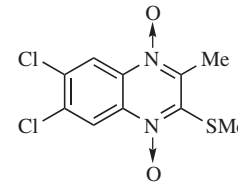
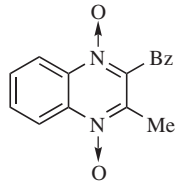
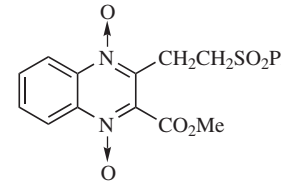
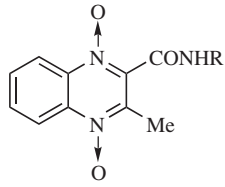
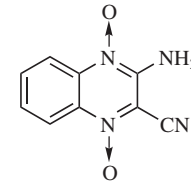
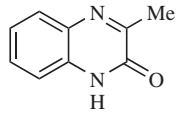
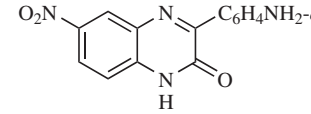
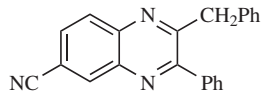
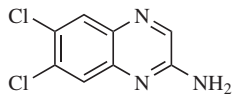
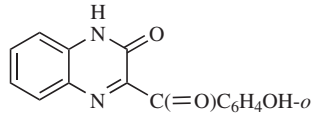
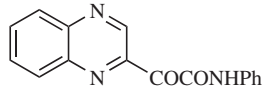
Section	Typical Products	
1.1.2.3		
		
1.1.3		
1.2.1		
1.2.2		
1.2.3.1		
		
1.2.3.2		
		

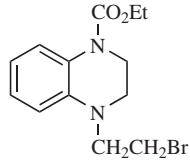
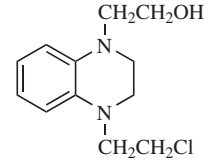
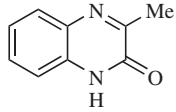
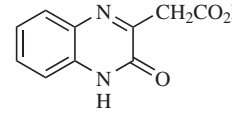
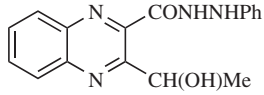
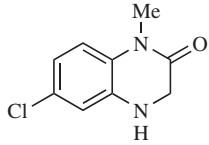
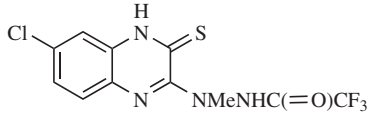
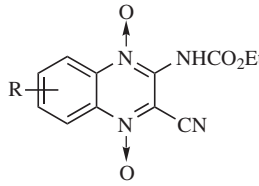
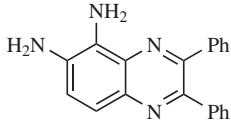
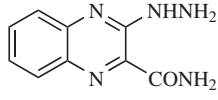
Section	Typical Products	
1.2.3.3		
1.2.3.4		
1.2.3.5		
1.2.3.6		
		
		
		
1.2.3.7		

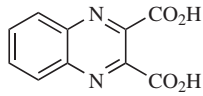
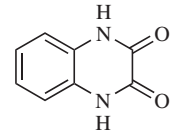
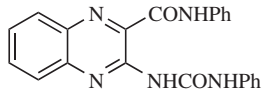
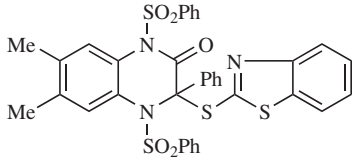
Section	Typical Products	
1.2.3.8		
1.2.3.9		
1.2.3.10		
1.2.3.11		
1.2.3.12		
1.2.3.13		
1.2.3.14		
1.2.4		
1.2.5		

Section	Typical Products	
		
1.3		
1.4		
1.5.1		
1.5.2		
1.5.3		
1.5.5		
1.5.6		
1.5.7		

Section	Typical Products	
1.5.8		
1.5.11		
1.5.13		
1.5.15		
1.6.1		
1.6.2		
1.6.3		
1.6.4		
1.6.5		

Section	Typical Products
1.6.7	 
	 
	 
1.6.9	 
1.7.1	
1.7.4	
1.7.5	
1.7.7	

Section	Typical Products
1.7.9	 
1.7.10	 
1.7.11	
1.7.13	
1.7.15	
1.7.16	
1.7.17	
1.7.19	

Section	Typical Products	
1.7.20		
1.7.21		
1.7.23		
1.8