3,4-Dihydroquinoxalin-2-ones: recent advances in synthesis and bioactivities (microreview)

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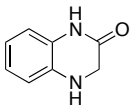
Abstract



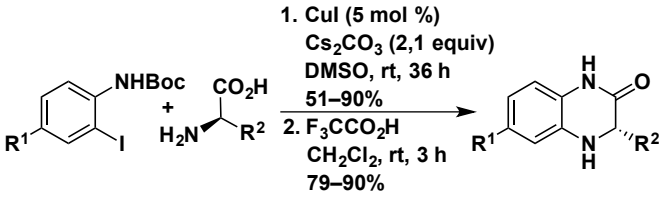
A summary of recent synthesis approaches to 3,4-dihydroquinoxaline-2-ones is discussed herein along with highlights of biological activity. The synthetic approaches include access to enantiopure heterocycles from chiral pool amino acids via coupling/cyclization, Michael addition/cyclization cascades, 3,3-disubstituted systems from multicomponent couplings, Bargellini reaction or photochemical reduction. The heterocycle displays notable antiviral and anti-inflammatory activities.

Introduction

The dihydroquinoxaline-2-ones are bicyclic, benzene-fused ketopiperazines with the carbonyl group in the 2-position.[1,2] They are of broad interest due to their potential medicinal properties, particularly antiviral and anti-inflammatory properties, as demonstrated in several studies.[3–5] Furthermore, this heterocyclic scaffold is particularly chemically versatile since multiple diversification strategies can be employed to produce a broad range of substitution patterns. In this microreview, we have surveyed the literature covering 2011–2016 emphasizing contemporary synthesis approaches to this valuable heterocycle, and as well as highlights demonstrating some of its biological activities that have been reported since 2000.

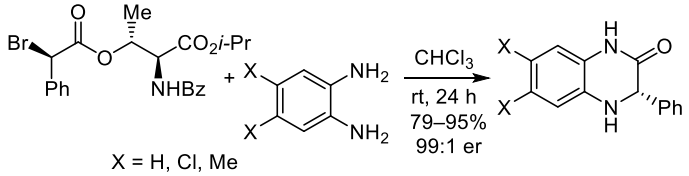
Enantiopure dihydroquinoxalin-2-ones

De Brabander et al. have reported the synthesis of 3-substituted dihydroquinoxaline-2-ones *via* a mild Ullmann-type, ligand-free amination of enantiopure α-amino acids with *N*-Boc-2-iodoanilines followed by cyclization.[6] The coupling reaction worked well with moderate to good yields (51-90%) with the exception where the amino acid containing the strongly electron withdrawing *para*-trifluoromethylphenyl group. Both methyl and cyano substituents on the iodoaniline, as well as unsubstituted iodoaniline were tolerated. Upon treatment with TFA the coupling products were converted into substituted dihydroquinoxalin-2-ones in good yields (79-90%) for all substrates. Both the coupling reaction and the cyclization occurred without racemization, and the dihydroquinoxalin-2-ones were isolated in excellent enantiomeric excess (>98% ee).



R^1 = H, Me, CN, R^2 = Ph, 6-ClC_6H_4, 6-FC_6H_4, 2-ClC_6H_4, indol-3-ylmethyl, *i*-Pr, $PhCH_2$

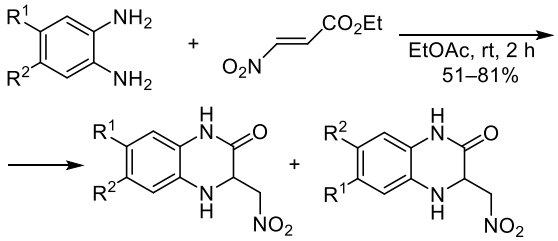
Park and co-workers recently demonstrated an asymmetric formation of substituted quinoxalin-2-ones through a chiral auxilliary approach.[7,8] A stereoselective substitution of enantiopure aryl α-bromo acetates with *o*-phenyldiamines was demonstrated, employing aryl α-bromo acetates enantioenriched through crystallization-induced dynamic resolution. The reaction yielded quinoxaline-2-ones in good to excellent yields (79-95%) and in excellent enantiomeric excess (99:1 er).



X = H, Cl, Me

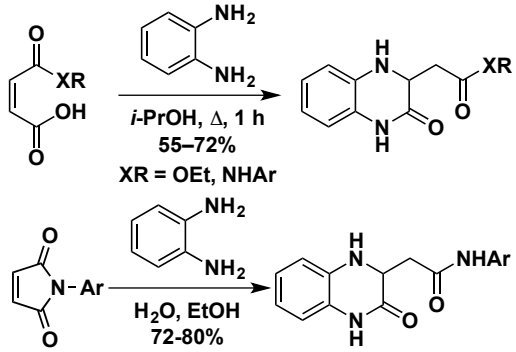
Michael addition strategies

A simple method for the synthesis of 3-nitromethyl substituted quinoxalin-2-ones was recently reported.[9] The reaction involves a Michael-addition/cyclization cascade process in which both symmetrical- and unsymmetrical *o*-phenylenediamines are used to obtain 3-nitromethyl substituted quinoxalin-2-ones in moderate to good yields (51-81%). Reactions with unsymmetrical *o*-phenylenediamines afforded regioisomeric mixtures without notable selectivity. Upon refluxing in aqueous solution, the nitromethyl group eliminates, yielding the corresponding quinoxalin-2(1*H*)-ones.



$R^1 = R^2 = H$, Me, Cl; R^1 = Me, Cl, $R^2 = H$

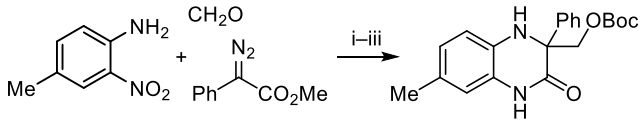
Rozhkov and coworkers demonstrated a different Michael addition approach, in which the reaction of *o*-phenylenediamine with maleic acid derivatives afforded 3-substituted 3,4-dihydroquinoxalin-2-ones in moderate to good yields (55-72%).[10] The reaction also works also with diethyl maleate and cyclic anhydrides. By employing the Michael addition strategy starting with pyrrole-2,5-diones, they were able to achieve generally higher yields of the desired heterocycle (72-80%)



Ar = Ph, 4-MePh, 4-EtPh, 2-ClPh, 2-NO_2Ph, 4-MeOPh

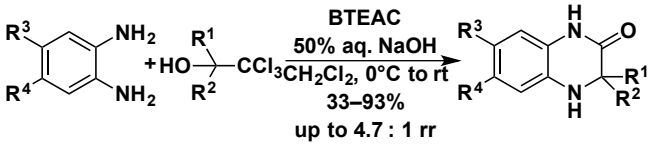
3,3-Disubstituted quinoxalin-2-ones

Hu and co-workers presented an effective Rh(II)-catalyzed three-component coupling method for producing α-aryl serine derivatives by trapping carbene-ammonium ylids with formaldehyde.[11] Further it was demonstrated that the α-serine product, upon Boc-protection and subsequent Pd-catalyzed hydrogenolysis, gives 3,3-disubstituted quinoxalin-2-one in overall 54% yield for the sequences. Although only one example of this was presented, the method is of potential high interest for the synthesis of 3,3-disubstituted systems.



i: $Rh_2(OAc)_4$ (1%), THF, 30°C, 58%; ii: $(Boc)_2O$, DMAP, Et_3N, CH_2Cl_2, rt, 12 h, 98%; iii: H_2, 5% Pd/C, MeOH, 95%

Recently Stokes and co-workers demonstrated the formation of 3,3-disubstituted dihydroquinoxalin-2-ones using the Bargellini reaction of *o*-phenylenediamines and substituted trichloromethylcarbinol electrophiles under phase-transfer conditions.[12] The reaction works with differently substituted trichloromethylcarbinols resulting in racemic products and can be extended to heteroatom-containing substrates as well as spirocyclic systems. The best yields were observed with methyl groups on the trichloromethylcarbinol. A variety of electronically diverse phenylenediamines could be employed in moderate to excellent yields (33-93%). For unsymmetrical diamines, the regioselectivity was generally low, but up to 4.7 : 1 ratio could be achieved with electron-withdrawing substituents. Notably, the regioselectivity switched when going from electron-donating to electron-withdrawing substituents.

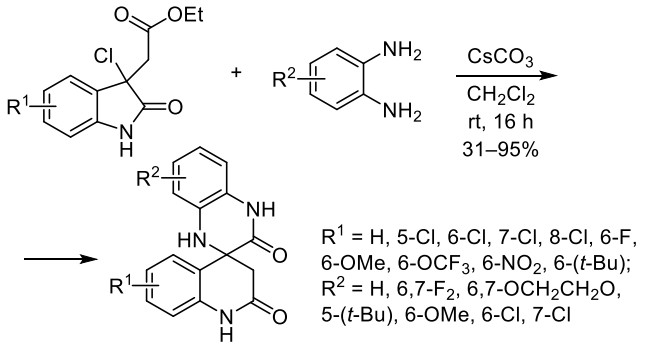


BTEAC - *N*-benzyl-*N*,*N*-diethylethanaminium chloride
R^1 = Me, Et, $(CH_2)_2$Ph, *cyclo*-Pr, CH_2OMe; R^2 = Me, H;
$R^1 = R^2 = (CH_2)_4$, $(CH_2)_2N(Boc)Me$, $(CH_2)_2O(CH_2)_2$;
R^3 = H, Me, Cl, Br, OMe, *t*-Bu, CF_3, CN, NO_2, R^4 = H, Me, Cl

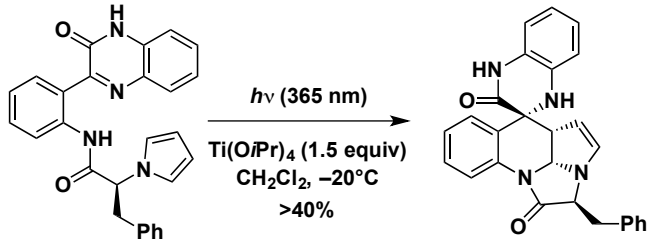
Spirocyclic quinoxalin-2-ones

Zou and coworkers reported a clever approach for synthesis of spirocyclic 3,4-dihydroquinoxalin-2-ones in moderate to excellent yields (31-95%) under mild conditions through a condensation of α-chlorooxoindoles with *o*-phenylenediamines.[13] The reaction proceeds by initial ring opening of the oxoindole by the diamine, followed by double cyclization to generate the spirocyclic system. A variety of substitution patterns were tolerated both on the oxoindole and the phenylenediamine

substrates.



Kutateladze and co-workers reported an exotic photoassisted intramolecular cycloaddition offering an alternative route to access spirocyclic quinoxalin-2-one scaffold incorporated into molecules with highly complex ring system.[14] Utilizing the photoactive core of quinoxalonone, and a pyrrole-containing unsaturated pendant based on L-phenylalanine, they demonstrated a stereoselective (4+2) cycloaddition resulting in enantiopure product (>40% yield). This represents an innovative synthetic approach to substituted enantiopure 3,4-dihydroquinoxaline-2-one systems starting directly from the fully oxidized quinoxaline-2(1H)-one system.



Highlights of biological activity

Several studies have established biological activities for 3,4-dihydroquinoxalin-2-ones.[3-5,15-16]

3,4-Dihydroquinoxalin-2-one GW420867X (Entry 1) has undergone clinical trials started in 2001. It was administered to HIV-1 infected patients, both alone and in combination with already approved HIV-1 drugs. The compound was well tolerated and displayed potent antiviral activity in this study.[17]

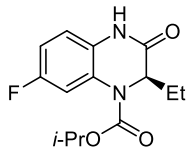
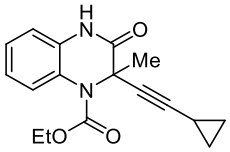
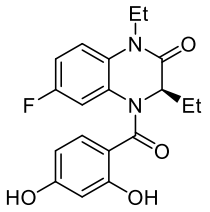
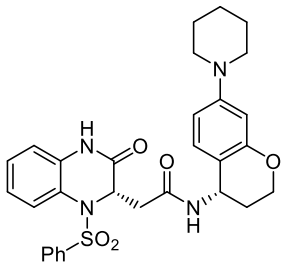
Patel and co-workers combined features from two potent HIV drug candidates to study the structure-activity relationships of hybrid structures such as 3-cyclopropylethynyl-4-ethoxycarbonyl-3-methyl-3,4-dihydroquinoxalin-2-one (Entry 2). The hybrids included structural elements inspired by the drug efavirenz, as well as the quinoxalin-2-one core of GW420867X. Although the compound displayed potency as a non-nucleoside reverse-transcriptase inhibitor (NNRTI), it was not further developed due to poor bioavailability in rhesus monkeys.[18]

Mahaney and co-workers studied several compounds containing the 3,4-dihydroquinoxalin-2-one core as estrogen receptor ligands. The two main types studied were with *N*-4 arylsulfonyl and benzoyl substitutions. Several of the derivatives tested displayed ligand potency, but compounds such as (*R*)-4-(2,4-dihydroxybenzoyl)-1,3-diethyl-6-fluoro-3,4-dihydroquinoxalin-2-one (Entry 3) yielded the best results.[19]

Chen and co-workers studied compounds of dihydroquinoxalin-2-one acetamides containing bicyclic amines as Bradykin B1 receptor antagonists. Previous studies have showed that 3-chloro-4-methyl substitution on the *N*-phenylsulfonamide was preferred. In this study, they mainly investigated different substituents at the piperidine ring and showed that a switch to more lipophilic groups (e.g. piperidine), instead of more simple amines, caused increased potency, while maintaining a simpler, unsubstituted phenylsulfonamide group (e.g. 2-((*S*)-2-oxo-4-(phenylsulfonyl)-3,4-dihydroquinoxalin-3-yl)-*N*-((*S*)-7-(piperidin-1-yl)chroman-4-yl)acetamide in Entry 4).[20]

Table 1. Biological activity of selected dihydroquinoxalin-2-ones

Compound	Mechanism of action	Target	Reported biological activity	Ref

1	 GW420867X	NNRTI	HIV-1	IC_{50} (μM): 179 IC_{90} (μM): 11	[17,18,21]
2		NNRTI	HIV-1	IC_{50} (μM): 118 IC_{90} (μM): 9	[18]
3		Estrogen receptor (ER) E2-NF_KB antagonist	Anti-inflammatory	IC_{50} (nM): 118 % E2-NF_KB: 92 EC_{50} (nM): 9 % E2-CK: 44	[19]
4		Bradykinin B1 receptor antagonist	Anti-inflammatory	K_I ± SEM(nM): 0.19±0.05 IC_{50} ± SEM(nM): 0.12±0.1	[20]

In summary, a range of innovative synthetic approaches has been described in recent years to obtain 3,4-dihydroquinoxalin-2-ones. Enantiopure 3-substituted systems can be generated from the chiral pool amino acids or by resolution techniques, whereas racemic complex spirocyclic structures can be accessed by photochemistry or clever rearrangements. The dihydroquinoxalin-2-ones display a range of biological activities, most notably anti-inflammatory and anti-viral actions. Moreover, this heterocycle possesses a range of opportunities for diverse functionalization and could therefore play an important role as a versatile scaffold for future drug design.

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Biographical sketches

Tone Kristoffersen was born in 1987 in Hammerfest, Norway. She is currently pursuing the Masters Degree in organic chemistry at UiT The Arctic University of Norway under the supervision of Assoc. Prof. Jørn H. Hansen. Her research interests include synthesis of heterocycles, applications of modern microwave methods in heterocyclic chemistry and development of chemical libraries for medicinal research.

Jørn H. Hansen received his Ph.D. in organic chemistry from Emory University (with Prof. Huw Davies) in 2010, followed by postdoctoral research at Princeton University (with Prof. David MacMillan), before joining UiT The Arctic University of Norway as an Associate Professor of Chemistry in 2012. His research interests range from development and applications of novel late-stage functionalization methods, chemical library design with bioactive and functional heterocycles, via computational mechanistic analysis to chemical education.