PREPARATION OF BIOMEDICALLY INTERESTING HETEROCYCLES STARTING FROM OXIRANIC COMPOUNDS

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Abstract. *Oxiranic compounds including nitroepoxides, cyanoepoxides, epoxyesters, epoxyketones and other functionalized epoxides have been transformed into diverse heterocycles. Mechanistically: the ring opening of the epoxide with selected nucleophiles including nitrogen functional groups, sulfur compounds and alkoxides affords an intermediate functionality which upon reaction with a second nucleophilic function gives rise to the corresponding heterocycle. Obtained compounds include four, five, six and seven-member ring heterocycles. These heterocycles are well known to display interesting biological and medicinal properties.*

Contents

1. Introduction

Heterocycles, particularly nitrogenated heterocycles, are among the most significant structural components of pharmaceuticals.[1] For example, quinoxaline derivatives have been reported as anticancer[2], antiviral,[3] antibacterial[4,5] and anti-inflammatory agents,[6] and as kinase inhibitors[7] and antibiotics.[8]

Compounds containing the pyrazine heterocycle are well known for their antiviral activities such as flavipiravir, a broad spectrum antiviral agent with activity against many RNA viruses;[9] antibacterial[9] and anti-inflammatory as tetramethylpyrazine (also known as ligustrazine).[10]

Compounds that possess a tetrahydroquinoxaline system have been studied as potent cholesteryl ester transfer protein inhibitors,[11] anticonvulsants,[12] potassium channel openers[13] and anti-HIV agents (Figure 1).[14]

The piperazine moiety has been classified as a "privileged scaffold" in medicinal chemistry.[15, 16]

Morpholine moiety is part of some commercial drugs, for example, of reboxetine (Eddronax, Prolift), a selective norepinephrine reuptake inhibitor (NRI);[17] phenmetrazine, a potent releaser of [^{3}H]norepinephrine and [^{3}H]dopamine;[18] phendimetrazine (Bontril), an anorexigenic drug;[19] and aprepitant (Emend), a potent and orally active NK1 receptor antagonist for chemotherapy-induced emesis, depression and other potential indications (Figure 1).[20]

Benzoxazine moiety is displayed by compounds with a wide range of biological activities such as neuroprotective agents,[21] PPARg agonists,[22] intracellular calcium antagonist,[23] antiangiogenic therapeutic agents,[24, 25] estrogen receptor β agonists[26] and antitumor.[27]

Benzodiazepine moiety has been classified as a "privileged scaffold" in medicinal chemistry and many bioactive compounds bear this core.[28]

Compounds containing tetrahydrobenzodiazepine moiety have found numerous applications in medicinal chemistry,[29] for example, BMS-214662 which exhibits potent antitumor activity (Figure 1).[30]

Compounds that possess imidazopyridine moiety display antitumor, antifungal, antibacterial, antiviral and antiprotozoal activities,[31] and some are currently marketed drugs such as Zolpidem, used for the treatment of sleep disorder, anxyolitic drug Alpidem[32] and antiulcer drug Zolimidine (Figure 1).[33]

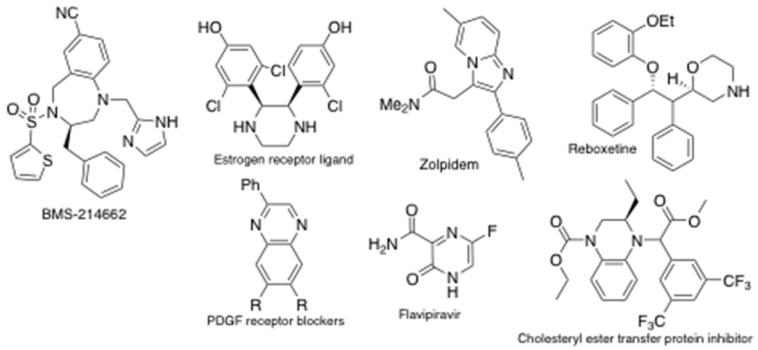


Figure 1. Examples of biologically active heterocycles**.**

Oxazole, pyrazole and imidazole derivatives display interesting biological properties. For example, oxazoles are antibacterial, antifungal, pesticidal, insecticidal, anti-inflammatory and antitumor.[34] Isoxazoles are also anticonvulsant, anticholestermic, antihelmintic, herbicidal and antimicrobial agents.[35] Imidazole derivatives display anticancer, antibacterial, antifungal, analgesic and anti-HIV properties.[36] Pyrazoles are medically interesting heterocycles with antitumor, antimicrobial, antidiabetic and anti-inflammatory activities.[37]

Pyrrole is one of the most important simple heterocycles, and many substituted or functionalized pyrrole derivatives are widely used in different fields.[38] In the pharmaceutical field, pyrrole ring, as an important structural unit, widely exists in natural and unnatural products showing different bioactivities such as antibiotics,[39] anti-HIV agents,[40] anti-inflammatory agents,[41] immunosuppressive and anticancer agents.[42]

The 2-aminoimidazole scaffold is present in a plethora of biological relevant molecules, displaying myriad potentially pharmaceutical properties,[43] such as human β-secretase inhibitors[44] and anticancer activity.[45]

Thiazoles are of eminent importance because of their potential as bioactive compounds[46] as ritonavir, a potent inhibitor of HIV protease.

Although above mentioned heterocycles have been accessed from different synthetic approaches, epoxides represent a valuable starting material for the preparation of these compounds (Figure 1). In this account, we summarize main endeavors about this topic including efforts made by our group during the last few years.

2. Synthesis of nitrogen heterocycles starting from nitroepoxides

Epoxides bearing a good leaving group such as nitroepoxides and cyanoepoxides display two highly oxidized vicinal positions which are exploitable as synthons with vicinal electrophilic centers (Figure 2).

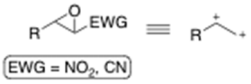
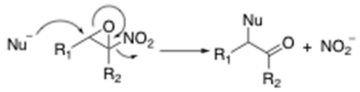


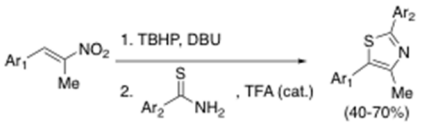
Figure 2. Epoxides as (+,+)-synthons.

Nitroepoxides were firstly described by Newman and Anger in 1969.[47] In this work, reactions between nitroepoxides with a series of representative nucleophiles were rationalized as a S_N2 mechanism,[48] in which the nucleophiles attack the beta position of the nitro group affording a ketone (Scheme 1).



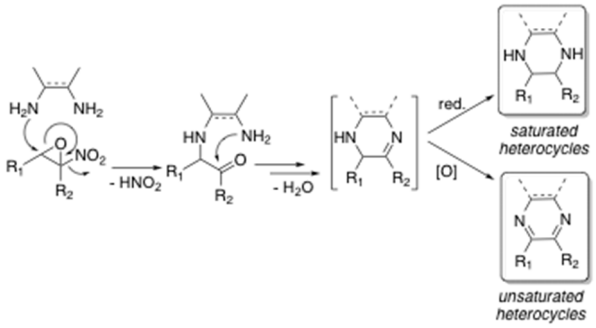
Scheme 1. Reaction of nitroepoxides with nucleophiles.

First work about the transformation of nitroepoxides into heterocycles was reported by Tsogoeva in 2011.[49] It represents a facile one-pot two-step process for the synthesis of 1,3-thiazoles via organocatalytic epoxidation of nitroalkenes followed by reaction of resulting nitroepoxides with thioamides (Scheme 2).



Scheme 2. Nitroalkenes into thiazoles.

In 2014, we reported a work about the preparation of a diverse group of 1,4-diamino heterocycles by treatment of nitroepoxides with diamines.[50] The reaction between nitroepoxide and 1,2-diamine affords an α-iminoamine intermediate which can be processed in two ways: the exposure to air produces the oxidized aromatic heterocycle, while the *in situ* addition of a reducing agent directly accesses the saturated analogue (Scheme 3).



Scheme 3. Conversion of nitroepoxides into diamino heterocycles.

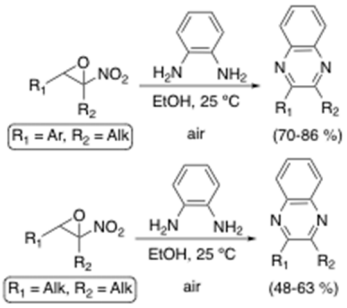
Quinoxalines are easily prepared by combining nitroepoxides with 1,2-benzenodiamine in ethanol as a solvent in the presence of air. Chemical yields are lower if nitroepoxides display an alkyl group in both positions (Scheme 4).

If nitroepoxides are treated with dry ammonia in methanol, pyrazines are obtained. Ammonia attacks the nitroepoxide to give an α-amino ketone which dimerizes to afford a dihydropyrazine intermediate which upon oxidation gives pyrazine (Scheme 5).

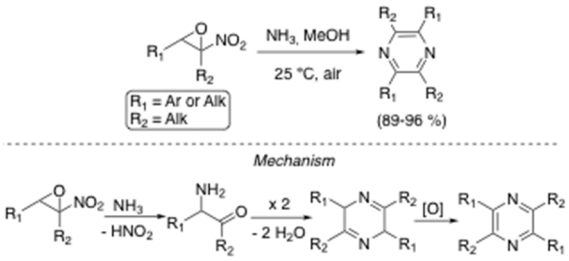
Piperazines were prepared by reaction between nitroepoxides and 1,2-ethylenediamine for six hours followed by addition of sodium triacetoxy borohydride as a reductive agent. The reaction afforded piperazines as a mixture of *cis/trans* isomers, with the *cis* isomer predominating. Stereochemistry was assigned by NMR studies (Scheme 6).

For the synthesis of tetrahydroquinoxalines, conditions were diferent to piperazines. Tetrahydroquinoxalines were prepared by reaction of nitroepoxides with 1,2-benzenodiamine in the presence

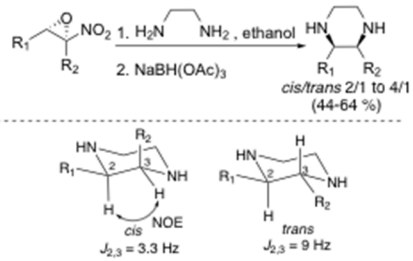
of air to obtain corresponding quinoxalines, and then, reduction with borane (Scheme 7).



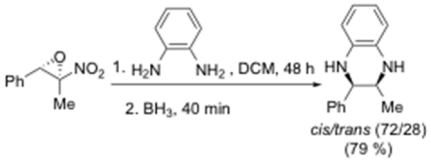
Scheme 4. Preparation of quinoxalines from nitroepoxides.



Scheme 5. Conversion of nitroepoxides into pyrazines.

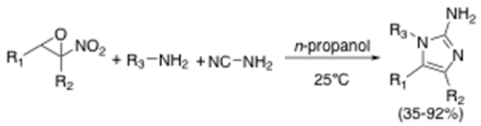


Scheme 6. Preparation of piperazines from nitroepoxides.



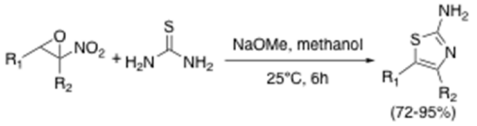
Scheme 7. Synthesis of tetrahydroquinoxalines from nitroepoxides.

In 2015, Yu and Zhang reported the regioselective preparation of 2-aminoimidazoles by reacting nitroepoxides with anilines and aminocyanamide in one-pot procedure (Scheme 8).[51] On the basis of experimental study, mechanism is proposed by ring opening of nitroepoxide with aniline to give the aminoketone. Then, the reaction of aminoketone and cyanamide would give rise to aminoimine intermediate. Finally, an intramolecular nucleophilic addition of the cyano group and subsequent tautomerization would give aminoimidazole.



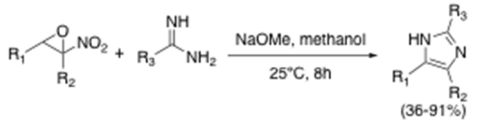
Scheme 8. One-pot procedure for the prearation of 2-aminoimidazoles.

Aminothiazoles can be prepared by reaction between nitroepoxides and thioureas using sodium methoxide in methanol, as same authors reported (Scheme 9).[52]



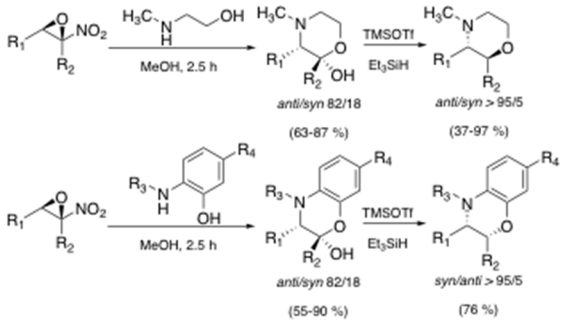
Scheme 9. Synthesis of aminothiazoles.

Yu has also recently reported the preparation of funtionalized imidazoles by reaction between nitroepoxides and amidines *via* an eco-friendly protocol (Scheme 10).[53] Sodium methoxide in methanol were best conditions.



Scheme 10. Preparation of functionalized imidazoles from nitroepoxides.

Morpholines and benzoxazines were prepared starting from nitroepoxides in our group.[54] The reaction between nitroepoxides and *N*-methylethanolamine in methanol afforded *anti*-morpholinols which upon treatment with trimethylsilyl triflate and triethyl silane gave *anti*-morpholines. Through a similar process, but using 2-hydroxyaniline instead of *N*-methylethanolamine, *syn*-benzoxazines were prepared (Scheme 11).

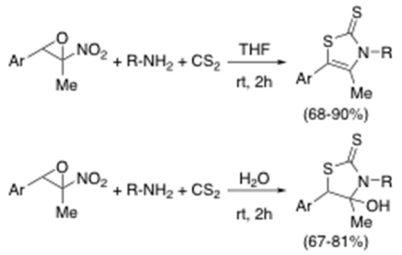


Scheme 11. Synthesis of morpholines and benzoxazines.

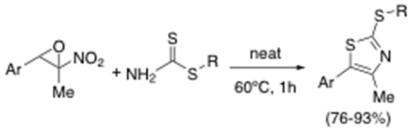
Halimehjani and Nosood have recently reported that *N,S*-heterocycles can be efficiently synthesized from nitroepoxides derived from nitrostyrenes.[55] Nitroepoxides were transformed into thiazole-2(*3H*)-thiones upon reaction with carbon disulfide and a primary amine in tetrahydrofuran as a solvent. Interestingly, the reaction affords corresponding thiazolidine-2-thiones if water is used instead (Scheme 12). The reaction mechanism starts by the formation of dithiocarbamic acid, followed by epoxide ring opening with the sulfur of the dithiocarbamate and intramolecular hemiaminalization.

On the other hand, if the reaction is done using previously prepared *S*-alkyl dithiocarbamates,

2-(alkylsulfanyl)thiazoles are obtained instead (Scheme 13).

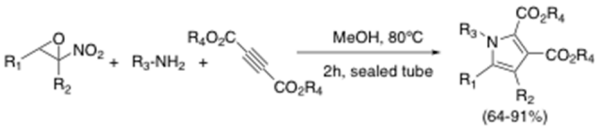


Scheme 12. Transformation of nitroepoxides into *N,S*-heterocycles.



Scheme 13. Preparation of *S*-alkyl dithiocarbamates.

Pentasubstituted pyrroles have been prepared starting from nitroepoxides through a three-component one-pot procedure.[56] Nitroepoxides displaying alkyl or aryl substituents react with aliphatic or aromatic amines in the presence of acetylene dicarboxylate furnishing pyrroles in good yield. Synthetic studies demonstrated that the mechanism of the transformation starts with the combination of nitroepoxide with the amine affording α-amino ketone, then, the attack of the nitrogen atom to the triple carbon-carbon bond of the acetylenic compound gives a vinyl anion which upon intramolecular addition to the ketone and dehydration affords aromatic pyrrole (Scheme 14).

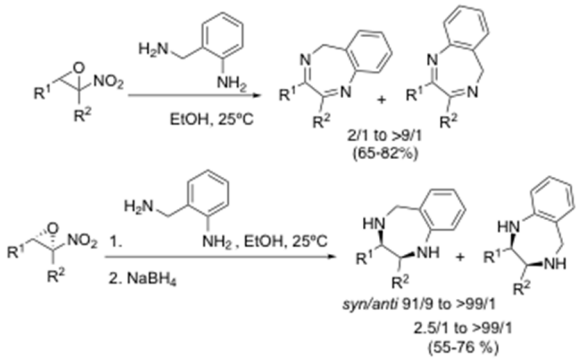


Scheme 14. Pentasubstituted pyrroles starting from nitroepoxides.

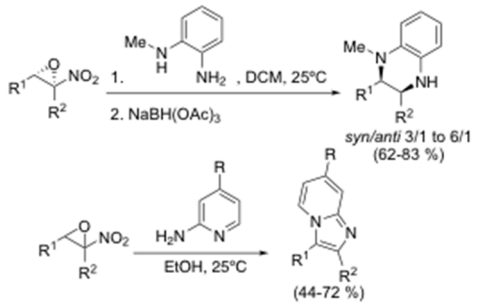
We have recently reported a work based upon the regioselective opening of nitroepoxides with unsymmetrical diamines to afford unsaturated heterocycles such as benzodiazepines and imidazopyridines, or saturated ones (tetrahydrobenzodiazepines, tetrahydroquinoxalines) if a reductive agent is added.[57] For example, when nitroepoxides are treated with 2-aminobenzylamine, then benzodiazepines are formed resulting from the initial attack of the aliphatic amino group to the β-position of the nitroepoxide. If sodium borohydride is added to the reaction mixture, tetrahydrobenzodiazepines are obtained in high stereoselectivity (Scheme 15).

Reaction of nitroepoxides with *N*-methyl-1,2-benzenodiamine and sodium triacetoxyborohydride affords *syn*-tetrahydroquinoxalines. In case of using 2-aminopyridines, imidazo[1,2-α]pyridines are formed (Scheme 16).

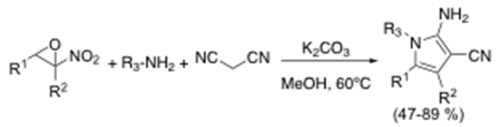
A synthesis of *N*-substituted 2-amino-3-cyano pyrroles via ring-opening of nitroepoxides has been recently reported by Yu (Scheme 17).[58] The process is a multi-component synthesis resulting from the combination of a nitroepoxide, an amine and malononitrile. Potassium carbonate in methanol resulted to be the best conditions. Synthetic studies were performed demonstrating that the key intermediate in the mechanism is the aminoketone formed between the nitroepoxide and the amine.



Scheme 15. Preparation of benzodiazepines and tetrahydrobenzodiazepines.



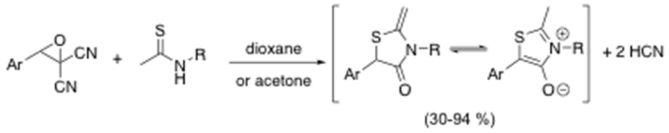
Scheme 16. Synthesis of tetrahydroquinoxalines and imidazopyridines from nitroepoxides.



Scheme 17. Amino cyano pyrroles from nitroepoxides.

3. Synthesis of thiazoles, piperidones and quinoxalines starting from cyanoepoxides

First example in the literature regarding to the conversion of cyanoepoxides into heterocycles is the one reported by Robert in 1976.[59] Mesoionic thiazoles are obtained in good yield by the reaction of *gem*-dicyanoepoxides with thioamides in a neutral media (Scheme 18).



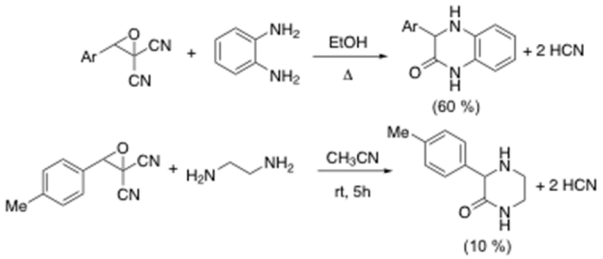
Scheme 18. Preparation of mesionic thiazoles from cyanoepoxides.

gem-Dicyanoepoxides have also been converted into tetrahydroquinoxalones by reaction with 1,2-benzenodiamine[60] and piperazones by reaction with 1,2-ethylenediamine[61] (Scheme 19).

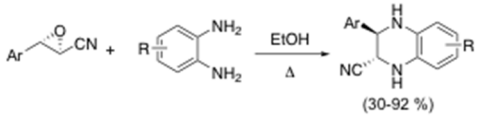
Under similar conditions cyanoepoxides give cyanotetrahydroquinoxalines when treated with 1,2-benzenodiamines (Scheme 20).[60] Interestingly, only *trans* isomers were obtained as determined by NMR.

Epoxy acylamidrazones, accessible from *gem*-dicyanoepoxides through 2-cyano-2-carbimidate

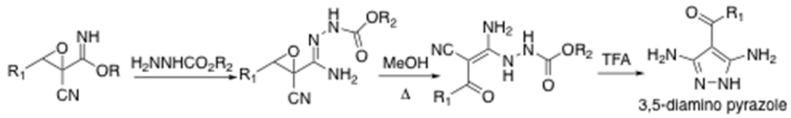
oxiranes,[62] can be converted into 3,5-diaminopyrazoles (Scheme 21).[63] Such compounds have been proved to be useful intermediates towards therapeutically interesting pyrazolo [1,5-α] pyrimidines.[64]



Scheme 19. Conversion of dicyanoepoxides into tetrahydroquinoxalones and piperazones.

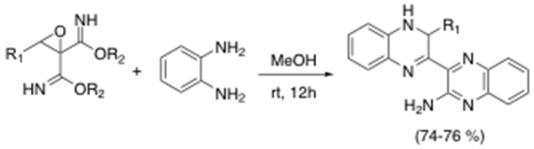


Scheme 20. Synthesis of cyanotetrahydroquinoxalines.



Scheme 21. Preparation of diamino pyrazoles.

2,2-Carbimidate oxiranes, which can be also prepared from *gem*-dicyanoepoxides, can be respectively converted into bisquinoxalines when react with 1,2-benzenodiamine (Scheme 22).[63]



Scheme 22. Synthesis of bisquinoxalines.

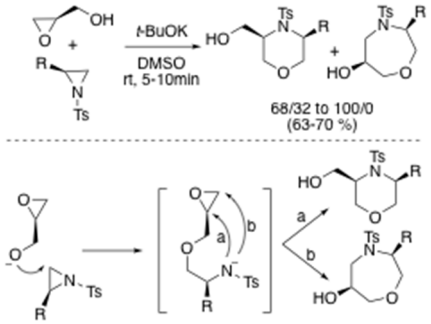
4. Synthesis of morpholines starting from epoxides

One pot synthesis of chiral disubstituted morpholines and 1,4-oxazepanes was reported through basic treatment of *R*-glycidol followed by addition of chiral aziridines derived from *S*-amino acids.[65] A plausible mechanism was proposed by highly regioselective aziridine ring opening by glycidol derived alcoxide, then, resulting nucleophilic nitrogen would open up oxirane ring following two possible pathways to form the desired molecules. Regioselectivity of the reaction depends on the substituent of chiral aziridine (Scheme 23).

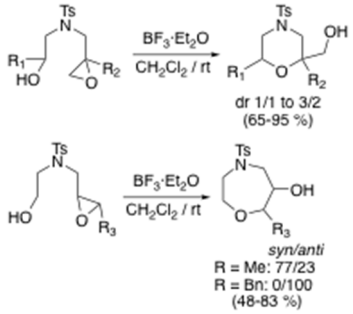
A new synthetic approach to morholines and 1,4-oxazepanes using nitrogen-tethered alkanol epoxides as starting material, has been reported.[66] Boron trifluoride etherate in stoichiometric amount is used as a Lewis acid. Regioselectivity of the reaction depends on the substitution of the oxirane ring (Scheme 24).

Recently, two groups have reported the total synthesis of spiromorpholine ring containing natural products acortatarins A and B through an oxiranic intermediate. In 2011, Sudhakar reported total synthesis, and also stereochemical revision, of acortatarins A and B.[67] Synthetic route proceeds through the deprotonation of substituted pyrrole with sodium hydride followed by *N*-alkylation via regioselective opening of terminal epoxides. Then, oxidation of the resulting secondary hydroxyl group furnished ketones

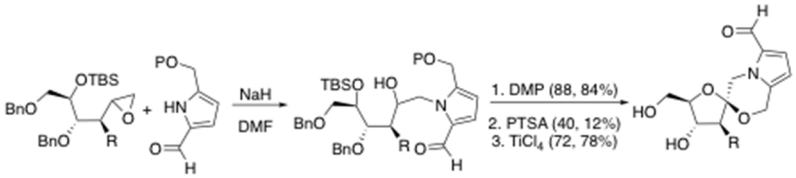
which were treated with *p*-toluenesulfonic acid resulting in deprotection and simultaneous intramolecular spiroketalization to give chromatographically separable mixture of anomers. Final debenzylation afforded desired natural products (Scheme 25).



Scheme 23. Preparation of morpholines and 1,4-oxazepanes.



Scheme 24. Preparation of morpholines and 1,4-oxazepanes.



Scheme 25. Synthesis of acortatarins A and B.

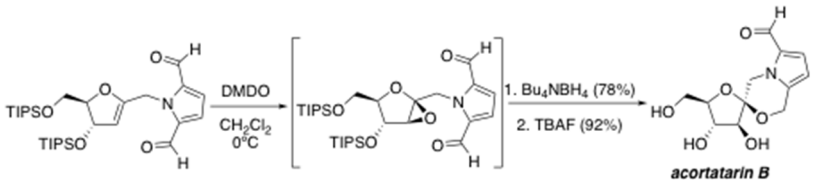
One year later, a stereoselective synthesis of acortatarin B[68] was accomplished by Tan through an epoxidation spirocyclization approach. Pyrrole dicarboxaldehyde intermediate underwent chemoselective β-epoxidation of the glycal with DMDO to form the putative epoxide. Tetrabutylammonium borohydride in dichloromethane provided the desired β-spiroketalic morpholine which upon deprotection afforded acortatarin B in excellent yield and diastereoselectivity (Scheme 26).

Recently, Marlin has reported a stereoselective synthesis of 2,3-disubstituted morpholines using a base-catalysed cascade reaction, starting from chiral epoxides.[69] The key step involves a one-pot oxazolidinone formation via intramolecular epoxide opening and concomitant cyclisation to form the morpholine ring (Scheme 27).

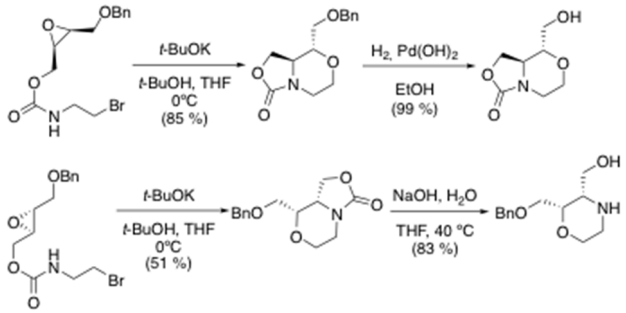
5. Synthesis of quinoxalines, tetrahydroquinoxalines and pyrazines starting from epoxides

In 2002, Duñach reported the synthesis of quinoxalines and tetrahydroquinoxalines by reaction

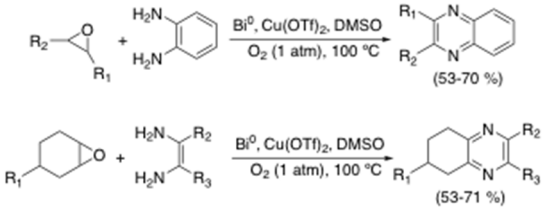
between epoxides and benzene-1,2-diamine or ene-1,2-diamines (Scheme 28).[70] The reaction proceeds in DMSO under molecular oxygen in the presence of catalytic amounts of Bi(0) and of copper triflate. Authors suggest that the mechanism proceeds via a diketone, which upon reaction with diamine would afford final product. The formation of the diketone would proceed in two steps: firstly formation of hydroxyketone by reaction between the epoxide and DMSO with the Lewis acid, and secondly oxidation of the hydroxyketone into the diketone by the Bi(0)/O_2 system, in a Bi(III)/Bi(0) redox process.



Scheme 26. Synthesis of acortatarin B.

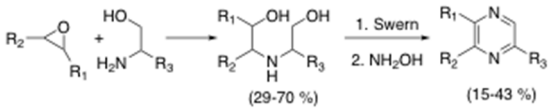


Scheme 27. Synthesis of disubstituted morpholines from chiral epoxides.



Scheme 28. Synthesis of quinoxalines and tetrahydroquinoxalines.

Taber studied the conversion of epoxides into pyrazines.[71] Representative epoxides were submitted to reaction with 1,2-aminoalcohols resulting into aminodiols which upon Swern oxidation followed by treatment with hydroxylamine gave corresponding pyrazines (Scheme 29).

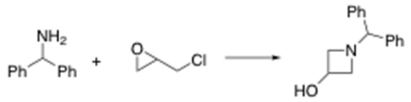


Scheme 29. Reaction of epoxides with aminoalcohols to give pyrazines.

6. Synthesis of azetidines starting from epoxides

Epichorohydrin has been transformed into a pharmaceutically interesting azetidinol upon chemical reaction with diphenylmethananime (Scheme 30). The transformation has been patented three times using

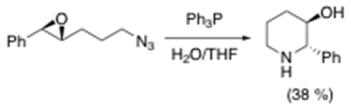
different conditions: HCl in DMF,[72] methanol for 72 hours[73] and sodium carbonate in isopropanol under reflux.[74]



Scheme 30. Epichlorohydrin to azetidinol.

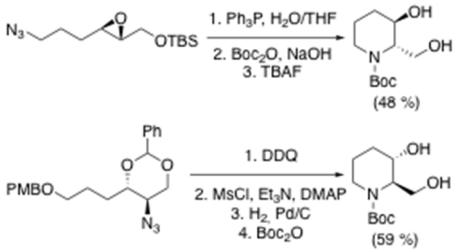
7. Synthesis of piperidines and pyrrolidines starting from azidoepoxides

An enantioselective synthesis of *trans*-hydroxypipecolic acid has been reported involving a regioselective intramolecular nucleophilic substitution of the amine derived from an azido epoxide through a Staudinger reaction as the key step (Scheme 31).[75]



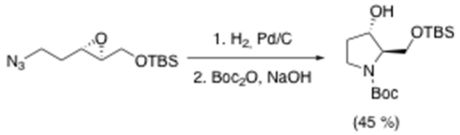
Scheme 31. Synthesis of piperidines.

A similar approach was used more recently by Kumar for the enantioselective synthesis of one of the enantiomers of *trans*-hydroxypipecolic acid (Scheme 32).[76]



Scheme 32. Enantioselective syntheses of piperidines.

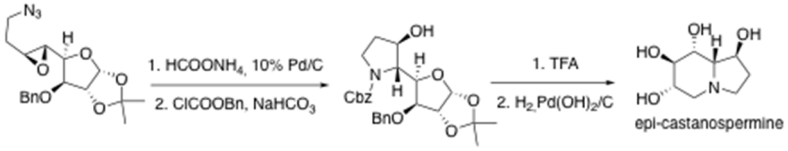
The same reaction, but using as a starting material a compound with one less carbon atom gave corresponding pyrrolidine which was converted into 3-hydroxy proline aminoacid (Scheme 33).[77]



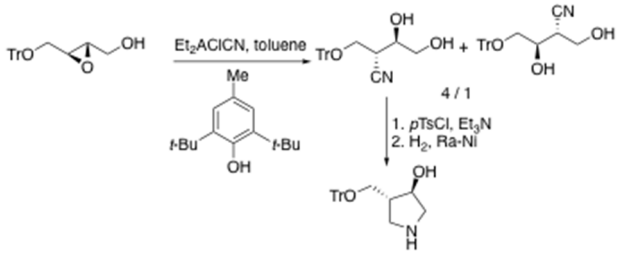
Scheme 33. Synthesis of pyrrolidines.

In addition, a Staudinger reaction of an azidoepoxide was used to construct the pyrrolidine ring as a key step towards the total synthesis of an epimer of the natural product castanospermine by Dhavale (Scheme 34).[78]

Five-membered azasugar derivatives are potent glycosidase inhibitors. An iminosugar was obtained by Ichikawa from fumaric acid monoester employing Sharpless asymmetric epoxidation followed by a Lewis acid-catalyzed epoxide ring-opening reaction (Scheme 35).[79]



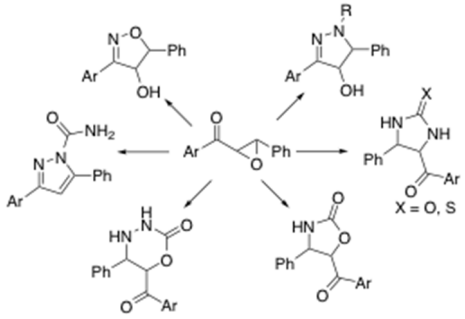
Scheme 34. Reaction with azidoepoxide as a key step to epi-castanospermine.



Scheme 35. Synthesis of azasugars.

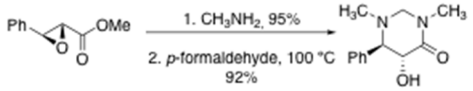
8. Synthesis of heterocycles starting from epoxyesters and epoxyketones

Epoxyketones have been converted into medically interesting heterocycles as pyrazoles, 1,2-oxazoles, ureas, thioureas, oxazolidines, oxadizines and pyrazole derivatives (Scheme 36).[80] Reactions were carried out under conventional thermal conditions and also by the use of grinding technique. The advantages of grinding technique over conventional approaches are the green, solvent free, safe conditions, as well as, its facile work-up, high-yielding and environmental friendliness.



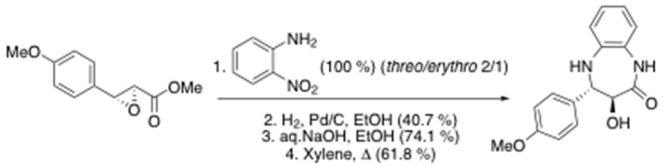
Scheme 36. Synthetic derivatizations of epoxyketones into heterocycles.

Pyrimidinones have been synthesized in two steps starting from epoxyesters.[81] The first step is the reaction of epoxyester with methylamine affording 2-hydroxy-3-methylamino propanamide which results into the corresponding pyrimidinone when treated with *p*-formaldehyde at high temperature (Scheme 37). This transformation was also studied from a theoretical view. *Ab initio* calculations support the idea that the cyclization step takes place under thermodynamic control.



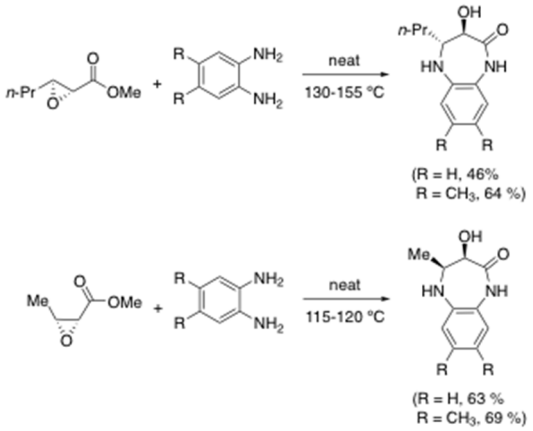
Scheme 37. Preparation of pyrimidinones from epoxyesters.

Epoxyesters have been also used for the synthesis of benzodiazepines. In 1985, Inoue reported a four-step sequence by reaction between phenylgycidates with 2-nitroaniline in the presence of zinc iodide to afford corresponding 3-amino-2-hydroxy ester, then, hydrogenation reaction for reductive conversion of the nitro group into aniline followed by alkaline hydrolysis of the resulting aminoester and lactamization gave 1,5-benzodiazepine derivative (Scheme 38).[82]



Scheme 38. Sequence for the conversion of epoxyesters into benzodiazepinones.

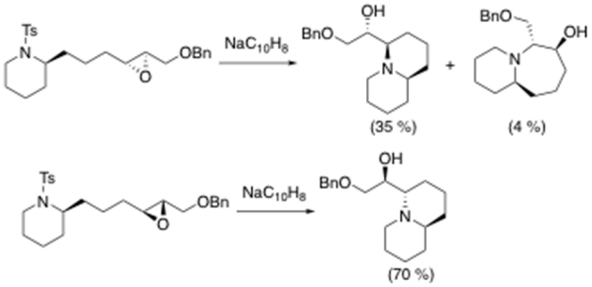
Enantiomerically pure glycidates have been transformed into optically active hydroxy benzodiazepinones upon reaction with 1,2-benzenodiamines under heating without solvent (Scheme 39).[83]



Scheme 39. Direct transformation of epoxyesters into benzodiazepinones.

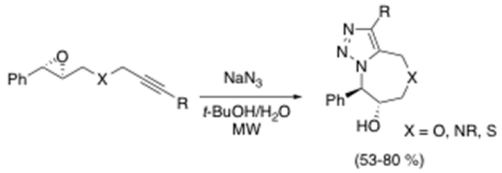
9. Other reactions involving synthesis of heterocycles from oxiranic compounds

It has been reported the construction of a quinolizidine ring system through an intramolecular regioselective ring opening of an epoxide by quaternization of the nitrogen atom of the piperidine moiety in the molecule.[84] The reaction takes place when *N*-tosylated precursor is submitted to reaction with sodium naphtalenide. Regioselectivity depends on the stereochemistry (Scheme 40).



Scheme 40. Quinolizidines from epoxides.

One-pot procedure for the conversion of 2-alkynyl derivatives of phenylglycidol into triazolooxazepinols, triazolodiazepinols and triazolothiazepinols was reported by Pericàs in 2011.[85] It is a two-step sequence: regioselective and stereospecific ring opening of epoxide with sodium azide followed by intramolecular metal-free Huisgen cycloaddition to afford corresponding bicyclic triazole (Scheme 41).



Scheme 41. Preparation of triazolooxazepinols, triazolodiazepinols and triazolothiazepinols.

10. Conclusion

It has been shown examples from the literature about the synthetic exploitation of oxiranic compounds for the preparation of biomedically interesting nitrogen heterocycles. Prepared heterocycles are four member (azetidines), five member (pyrrolidines and pyrroles), six member (pyrazines, piperidines and piperazines) and seven member rings (pyrimidinones, benzodiazepines and oxazepines). All this report evidences epoxides as versatile compounds for the preparation of these biomedically interesting compounds.

Acknowledgements

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