RECENT ADVANCES IN THE SYNTHESIS OF 1,2-BENZISOXAZOLES AND 1,2-BENZISOXAZOLINES

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Abstract. *The 1,2-benzisoxazole core is present in natural alkaloids and is used as a versatile building block in drug discovery because of the wide range of pharmacological activities. 1,2-Benzisoxazole-containing drugs such as zonisamide and risperidone have been used as anticonvulsants for decades. Although old synthetic methods for benzisoxazole core synthesis were efficient enough, development of organic chemistry inevitably led to the emerging of new approaches to this heterocycle moiety. This review covers classical and modern synthetic approaches to 1,2-benzisoxazoles, 1,2-benzisoxazolines and benzisoxazoline-3-ones that have been used in the last 25 years.*

Contents

1. Introduction

Heterocyclic compounds represent almost a half of the known organic compounds and exhibit diverse applications in medicine, agricultural chemistry, material science, and polymer chemistry.[1] Various nitrogen-containing heterocycles are the most widespread and extensively used in pharmacology.[2] Heterocycles with more than one heteroatom are of special interest as they demonstrate diverse biological activity. At the same time, they often require specific approaches for their synthesis. Many nitrogen heterocycles belong to the so-called “privileged” scaffolds for medicinal chemistry. Of particular importance are compounds possessing isoxazole core. These five-membered nitrogen-containing heterocycles possessing nitrogen and oxygen atoms at the adjacent positions, found various applications in technology, agriculture[3] and especially in medicine.[4,5] Their benzo-fused congeners 1,2-benzisoxazoles (benzo[d]isoxazoles, indoxazenes) demonstrate antifungal, antibacterial, anticancer, anti-inflammatory, anti-HIV activities,[6,7] and can be used for crop protection.[8,9] Benzisoxazole-containing compounds are presented in natural sources. Thus, naphtho-fused zwitter-ionic isoxazole alkaloid Fusaravenin **1** was

isolated from the extracts of the soil fungus *F. avenaceum* SF-1502 (Figure 1).[10] Simple alkaloid **2** (3,6-dihydroxy-1,2-benzisoxazole) was obtained from isolates of *Chromobacterium violaceum* and exhibited selective activity against Gram-negative bacteria.[11] Synthetic benzisoxazole derivative **3** was identified as a PPARα/γ dual agonist with relative PPARα selectivity and can be potentially useful for the treatment of type 2 diabetes and dyslipidemia.[12,13] The benzisoxazole scaffold is present in some drugs such as anticonvulsant Zonisamide **4** that is used for the treatment of epilepsy and Parkinson's disease, and atypical antipsychotics Risperidone **5** and Iloperidone **6**, which are used to treat schizophrenia and bipolar disorder.[6,14,15] 2,3-Dihydro-1,2-benzisoxazoles (1,2-benzisoxazolines) are also found in nature. Polycyclic alkaloid hypodemapyrazine **7**, which was extracted from the fern *Hypodematium sinense*,[11] and various synthetic *N*-arylated benzisoxazolines demonstrate antimicrobial activity.[16,17]

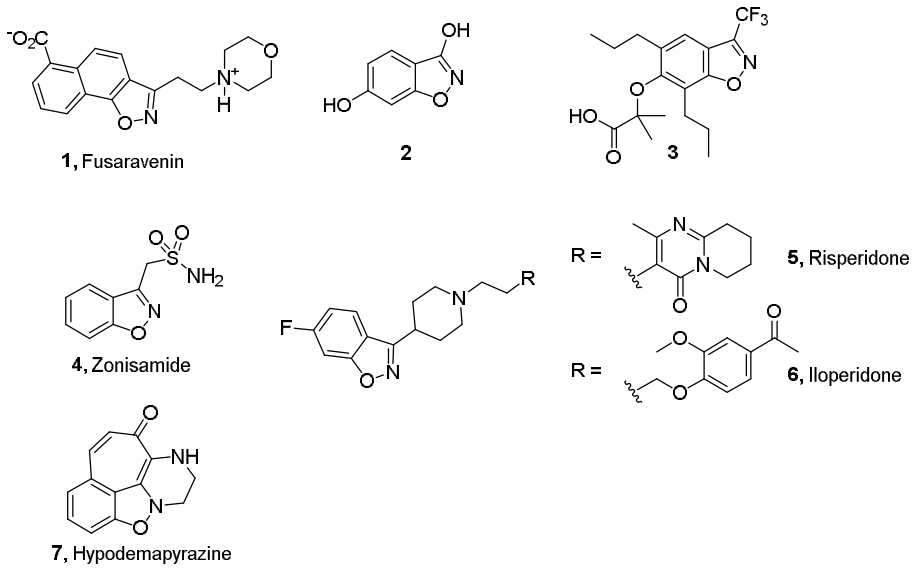


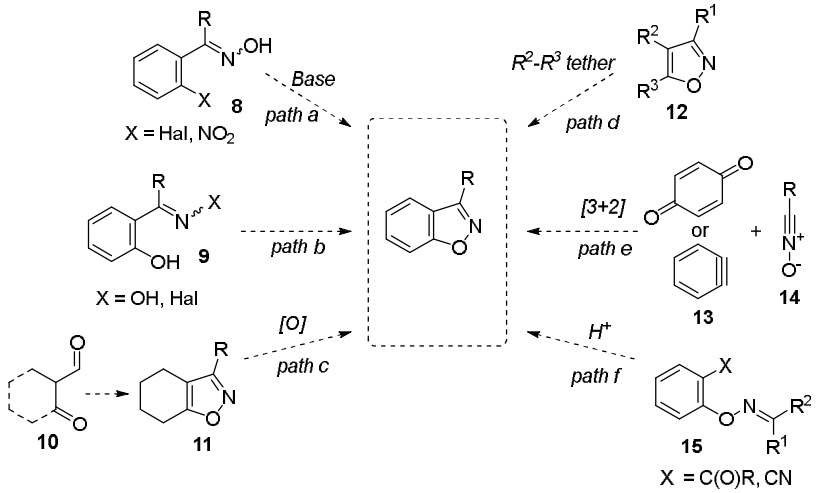
Figure 1. Some biologically active compounds with 1,2-benzisoxazole (1,2-benzisoxazoline) scaffold.

A previous comprehensive review on 1,2-benzisoxazoles and related compounds was published 25 years ago by Gualtieri and Giannella.[18] It covered the literature up to 1999. A lot of synthetic methods described in this paper are still used nowadays, although new efficient approaches to these heterocyclic systems have appeared. Moreover, the development of transition-metal catalyzed coupling reactions and growth of the aryne chemistry led to the appearance of new methods for benzisoxazole preparation. This review provides an update on the recent advances in the synthetic approaches to the benzisoxazole core covering the period 1999-2024. The synthesis of 1,2-benzisoxazole and 1,2-benzisoxazolines will be discussed. The well-known old approaches that are still used by organic chemists will be briefly presented highlighting the recent examples. Modern approaches such as an aryne-based cycloaddition reactions and metal-catalyzed annulations will be discussed in more detail.

2. Synthesis of 1,2-benzisoxazole core

There is a variety of methods for benzisoxazole synthesis that allow to obtain the target heterocyclic scaffold from different precursors. Traditional approaches to 1,2-benzisoxazole core are based on five-membered ring construction. They involve either synthesis *via* C–O bond formation (Scheme 1, *path a*) or *via* N–O bond formation (Scheme 1, *path b*). In the first case, cyclization is usually performed under basic conditions starting from *o*-substituted aryl oximes **8**. In the second case, *o*-hydroxyaryl oximes or *o*-hydroxy-*N*-subsituted aryl imines **9** serve as starting materials. It is important that substrates **8** and **9** can be easily obtained from corresponding carbonyl compounds, thus making these synthetic methods most

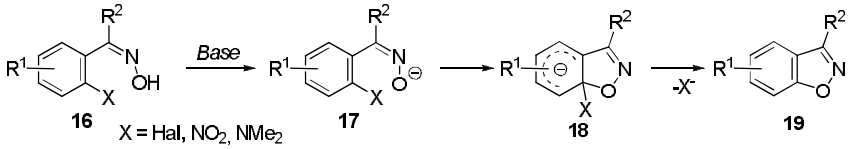
employed for preparing benzisoxazoles. Some approaches based on oxidizing reactions allow synthesizing benzisoxazole core from partially hydrogenated derivatives (e.g., cyclohexane-fused isoxazoles **11**), which can be prepared from 1,3-dicarbonyl compounds **10** (*path c*). Benzene ring closure approach provides benzisoxazole core from substituted isoxazoles **12** (*path d*). Simultaneous formation of C–C and C–O bonds was achieved using [3+2]-cycloaddition reactions of benzoquinones or arynes **13** with various 1,3-dipoles (*e.g.*, nitrile oxides **14**, *path e)*. Acidic treatment of *O*-aryl oximes **15** is a facile method for the synthesis of 3-amino- and other 3-substituted derivatives (C=N double bond formation, *path f*). Other synthetic approaches to 1,2-benzisoxazole core are also used and will be discussed below.



Scheme 1. General methods for 1,2-benzisoxazole synthesis.

2.1. C–O Bond formation. Synthesis from *o*-substituted aryloximes

Base promoted ring-closure to five-membered ring by treatment of aryloximes **16** bearing leaving group in *ortho*-position is one of the oldest approaches,[18] yet it is still used for the construction of benzisoxazole core (Scheme 2). To accomplish the cyclization substrates **16** are treated with a base (K_2CO_3, KOH, *t*-BuOK, etc.) in polar solvents (alcohols, dioxane, THF, DMF, etc.). However, base-free cyclization of 2-haloaryl oximes was reported by heating in PEG-600 under microwave irradiation.[19] The commonly accepted mechanism starts with the deprotonation of –OH group with formation of oxime anion **17**. Subsequent intramolecular *O*-attack on the *ortho*-position of aromatic ring and elimination of X-anion from **18** produces the target heterocycle core **19** *via* nucleophilic aromatic substitution (S_NAr). In agreement with the mechanism, electron-donating substituents in the aromatic ring reduce the reactivity of these substrates, whereas the electron-withdrawing substituents facilitate the cyclization.

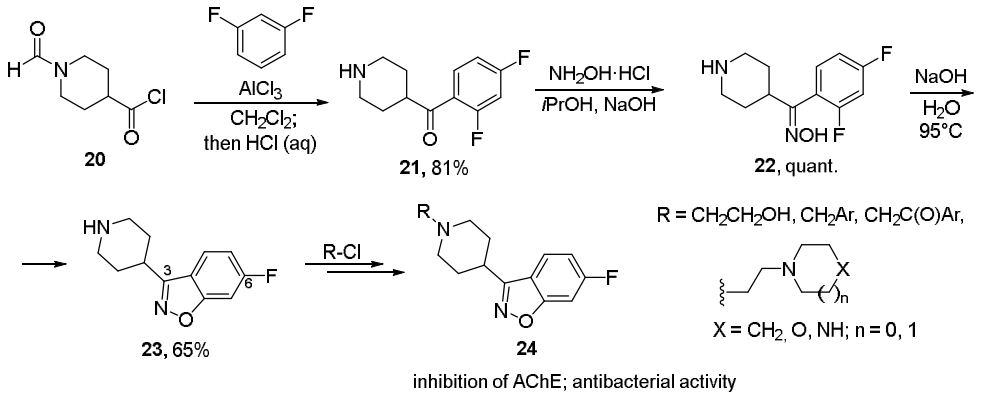


Scheme 2. General scheme for the synthesis of benzisoxazoles **19** *via* cyclization of oximes **16**.

The reactivity of *o*-substituted aryl oximes **16** depends on the nature of the leaving group. Fluoro derivatives (X=F) demonstrate the highest reactivity, albeit other halogen-substituted oximes (X=Br, Cl) as well as *o*-nitroaryl oximes ($X=NO_2$) can be used. Although dimethylamino group is known to be a poor nucleofuge, one example of cyclization of *o*-dimethylamino oximes ($X=NMe_2$) has been reported.[20] Another

key factor of the cyclization reaction is the configuration of the starting oxime **16**. Literature data demonstrate that only the *Z*-isomer reacts to form benzisoxazole ring, while the *E*-isomer produces side products.[18,21] Nevertheless the possibility of oxime isomerization under the reaction conditions should be taken into account, thus *E/Z*-oxime isomers mixtures are often used. This approach to benzisoxazole core is known for more than one century and remains to be one of the most common pathways to diverse benzisoxazole derivatives. Recent examples of this reaction and modifications of this procedure will be shown below.

Base-promoted ring closure in aryloximes was used as a simple and efficient method for the synthesis of biologically valuable 6-fluoro-1,2-benzisoxazoles.[22-24] For instance, starting *o*-fluoro oxime **22** was prepared from corresponding acid chloride **20** by Friedel-Crafts reaction followed by oximation of ketone **21** with hydroxylamine hydrochloride. The cyclization step was performed upon treatment with NaOH/H_2O at 95 °C and afforded 6-fluoro-benzisoxazole derivative **23** in good yield.[25] Flow synthesis in hot water for **23** was also reported.[26] Further reaction with various alkyl chlorides afforded wide scope of 3-substituted-benzisoxazoles **24** (Scheme 3), which were shown as potent acetylcholinesterase inhibitors and displayed antibacterial activity. A similar synthetic approach was used for the preparation of other 6-halo-3-substitued-1,2-benzisoxazoles that can be used as sodium channel blockers, anticonvulsant agents,[27] and new potential corrosion inhibitors.[28]



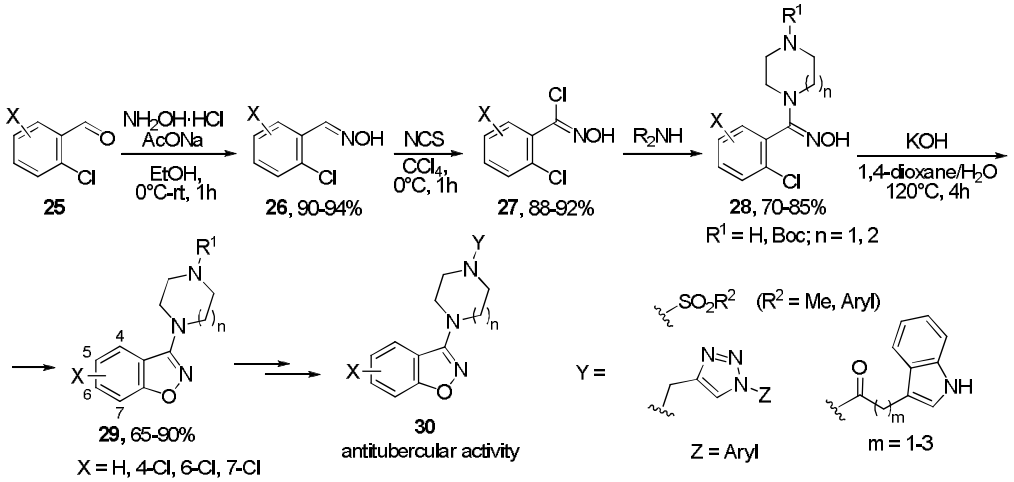
Scheme 3. Synthesis of 6-fluorobenzisoxazole derivatives **23** and **24**.

The base-promoted ring closure methodology is not limited to the synthesis of 3-alkyl substituted benzisoxazoles. This approach was modified for the preparation of biologically active 3-aminosubstituted derivatives,[29–31] and was used for the preparation of biologically active benzisoxazoles **29** bearing a cyclic amine at the C-3 (Scheme 4).[32-34] For this purpose, starting *o*-chloro-benzaldehydes **25** were converted into substituted 2-chloro-*N*-hydroxybenzimidoyl chlorides **27** *via* the reaction with hydroxylamine followed by chlorination of oxime **26** with NCS. Further substitution of chlorine by reaction with an excess of corresponding cyclic amines afforded the desired precursors **28**. Cyclization under basic conditions (heating with KOH in dioxane/water mixture) led to the formation of 3-aminosubstituted benzisoxazoles **29** in good yields. Subsequent derivatization afforded wide scope of biologically active compounds **30** containing sulfonyl, triazole, or indole fragment.

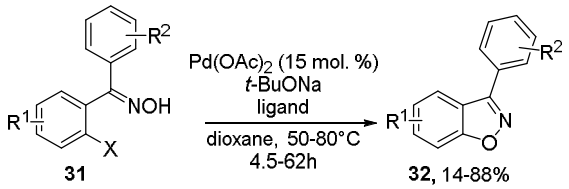
To avoid harsh reaction conditions such as high temperature, leaving group activation can be performed using transition-metal catalysis in an intramolecular cross-coupling mode. Thus, Pd-catalyzed cyclizations of *o*-substituted aryloximes **31** have been reported (Scheme 5).[35,36] The reaction of 2-haloaryl oximes (X=Cl, Br) and *t*-BuONa in the presence of $Pd(OAc)_2$ under gentle heating led to the formation of benzisoxazole **32** in excellent yields up to 88%. However, carrying out the cyclization of 2-ONf-aryloximes resulted in significant decrease in yield to 14%.[36]

The expensive palladium catalyst in this cyclization can be replaced with cheaper Cu(I) salts.[21,37] Tois *et al.*[21] performed the copper catalyzed cyclization of the *Z*-isomers of oximes in the presence of CuI.

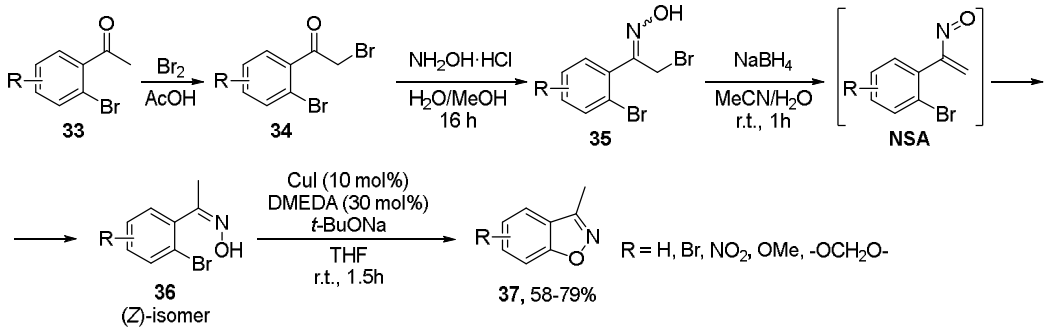
Starting *Z*-oximes **36** were selectively synthesized from the corresponding 2-bromoacetophenones **33** in three steps, namely, α-halogenation **33**→**34**, oximation **34**→**35**, and reduction with $NaBH_4$, presumably *via* nitrosoalkene intermediate **NSA** (Scheme 6). The cyclization step was performed under mild conditions through reaction with 10 mol% CuI and *N,N*'-dimethylethylenediamine (DMEDA) as the ligand at room temperature to give title heterocycles **37** in good yields. The authors demonstrated the catalytic nature of the transformation since treatment of *Z*-oxime with a base and DMEDA in the absence of copper salt did not lead to any benzisoxazole. However, cyclization occurred immediately after the addition of CuI. It was also noted that no *E*/*Z*-isomerization was observed under reaction conditions making the preparation of *Z*-substrates **36** important.



Scheme 4. Synthesis of benzisoxazole **29**.

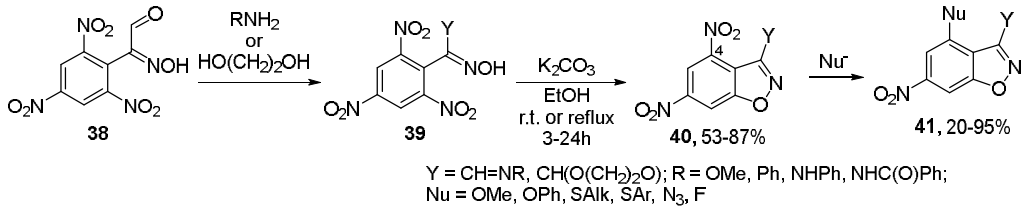


Scheme 5. Synthesis of benzisoxazoles **32** *via* Pd-catalyzed cyclization.



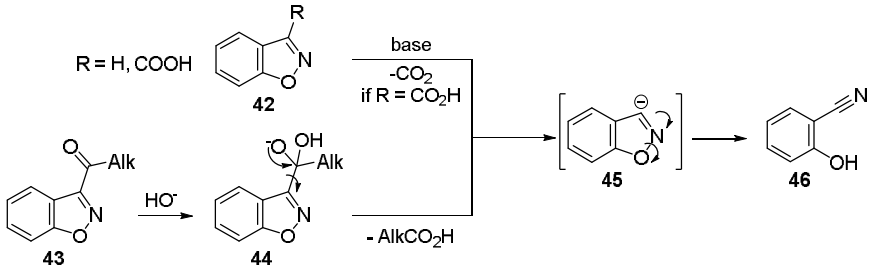
Scheme 6. Synthesis of benzisoxazoles **37** *via* (*Z*)-oximes **36**.

As mentioned above, benzisoxazole can be easily prepared from *o*-nitroaryloximes under basic conditions.[38,39] Shevelev *et al.*[39] reported that polynitroaryl oxime derivatives can be used as convenient substrates (Scheme 7). Starting from aldehydo-oximes **38**, the formyl group was firstly protected to obtain the imine or dioxolane derivatives **39**. Treatment of the corresponding protected oximes **39** with K_2CO_3 in ethanol led to displacement of the nitro-group, resulting in the formation of 4,6-dinitro-benzisoxazoles **40** in good yields. The obtained 4,6-dinitro-benzisoxazoles can be used as precursors for more complex heterocyclic systems, such as 4-nitro-6,7-furoxanobenzo[*d*]isoxazoles,[40] or can be modified by selective substitution of the nitro-group in the C-4 position with various nucleophiles, *e.g.* OAlk, OAr, SAlk, azide and fluoride to give derivatives **41**.



Scheme 7. Synthesis of benzisoxazoles **41** *via* nitroaryl-substituted oximes **39**.

Despite the great synthetic utility of based-promoted cyclization of *o*-substituted aryloximes, it has some limitations. For instance, this approach is poorly suitable for the synthesis of benzisoxazoles bearing substituents R in the C-3 position such as R=H, CO_2H **42**, and C(O)Alk **43** (Scheme 8). In this case, the initially formed benzisoxazole may suffer either proton abstraction or decarboxylation/deacylation **44** at C-3 with subsequent N–O bond cleavage in anion **45** (Kemp elimination) resulting in the formation of the corresponding salicylonitrile **46**.[18,41]



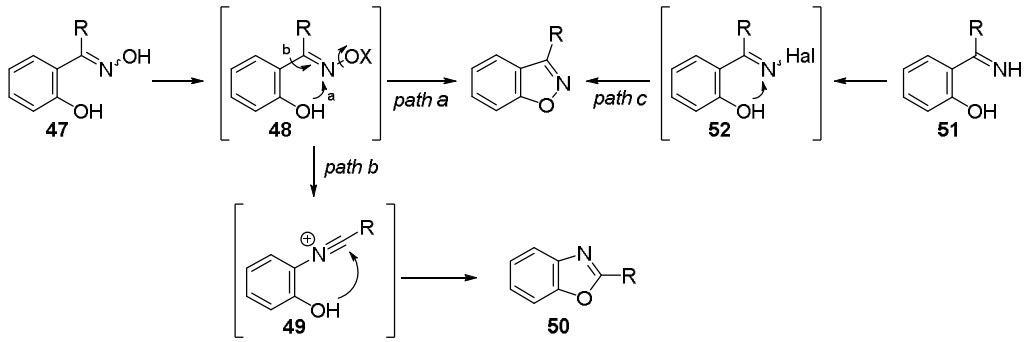
Scheme 8. Possible degradation paths of benzisoxazole derivatives *via* Kemp elimination.

2.2. N–O Bond formation. Synthesis from *o*-hydroxyaryl oximes and imines

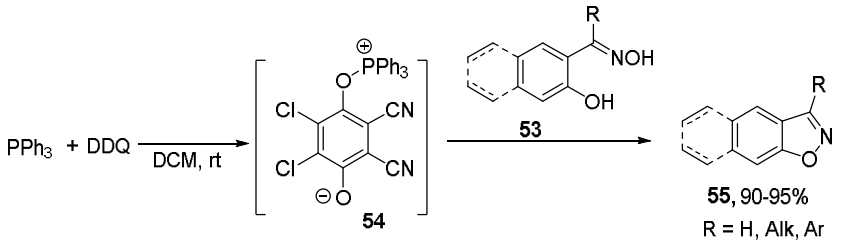
Synthesis of benzisoxazoles from 2-hydroxybenzoyl derivatives is the second most common approach. It relies on the nucleophilic substitution at the nitrogen atom by phenolic hydroxyl to produce the benzisoxazole core. Typically, two synthetic strategies are employed. The first is the cyclization of 2-hydroxyaryl oximes **47** *via* a formal dehydration reaction (Scheme 9, *path a*). The hydroxyl group of oxime is converted into a good leaving group OX by various reagents allowing subsequent cyclization. However, Beckmann rearrangement **48**→**49** can be a competitive process that leads to the formation of benzo[*d*]oxazoles **50** as side products (*path b*).[42-44] The second method uses cyclization of *N*-halogenated 2-hydroxyaryl imines **52**, obtained from corresponding imines **51** (Scheme 9, *path c*). In both cases, N–O bond formation occurs.

For the synthesis of benzisoxazoles from 2-hydroxyaryl oximes the main task is to activate an oxime hydroxyl group toward substitution. Thus, cyclization of 2-hydroxyaryl oximes into corresponding benzo- and naphthoisoxazoles can be performed by treatment with diethylchlorophosphate,[45,46] AgO in presence of *N*-methylmorpholine *N*-oxide,[47] CDI,[43,48] silica/Na_2CO_3 or under MW irradiation.[49,50] However,

one of the most common procedures is an intramolecular Mitsunobu reaction. Agents such as azodicarboxylates,[51,52] and phosphacumulenes ($R_3P{=}C{=}C{=}O$)[53] can be applied for this cyclization. A recent efficient modified approach utilized a combination of DDQ and PPh_3 that believed to proceed *via* adduct **54**.[54-57] Therefore, reactions of oximes **53** with PPh_3/DDQ afforded various benzo- and naphtho-fused isoxazoles **55** in excellent yields (Scheme 10).[54]

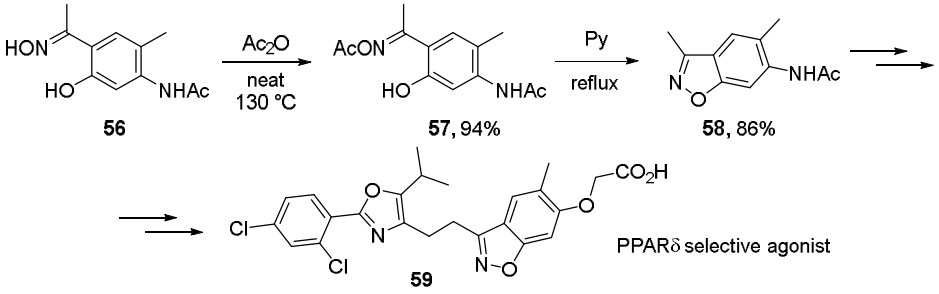


Scheme 9. General scheme for the synthesis of benzisoxazoles by cyclization of oximes **47** or imines **51**.



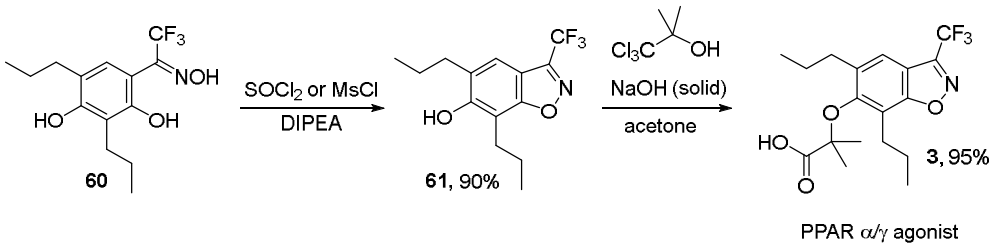
Scheme 10. Cyclization of oximes **53** using PPh_3/DDQ system.

Another method of the –OH group activation is its transformation into *O*-acyl fragment. In this case, sequential treatment of *o*-hydroxyaryl oximes with acylating agents and bases (commonly used triethylamine, pyridine, or sodium hydride) is applied. The most common two-step procedure involves reaction of hydroxy oximes with acetic anhydride, typically neat. Further treatment of *O*-acyl derivatives with a base produces benzisoxazoles in good yields.[9,58-62] This methodology was successfully used for the synthesis of benzisoxazole-containing human PPARδ selective agonist **59** (Scheme 11).[63] Thus, key intermediate benzisoxazole derivative **58** was prepared by sequential acylation of starting oxime **56** and cyclization of *O*-acyloxime **57** in pyridine. *O*-Acyl oximes have also been reported to undergo cyclization upon heating in vacuum[64] or under microwave irradiation.[65]



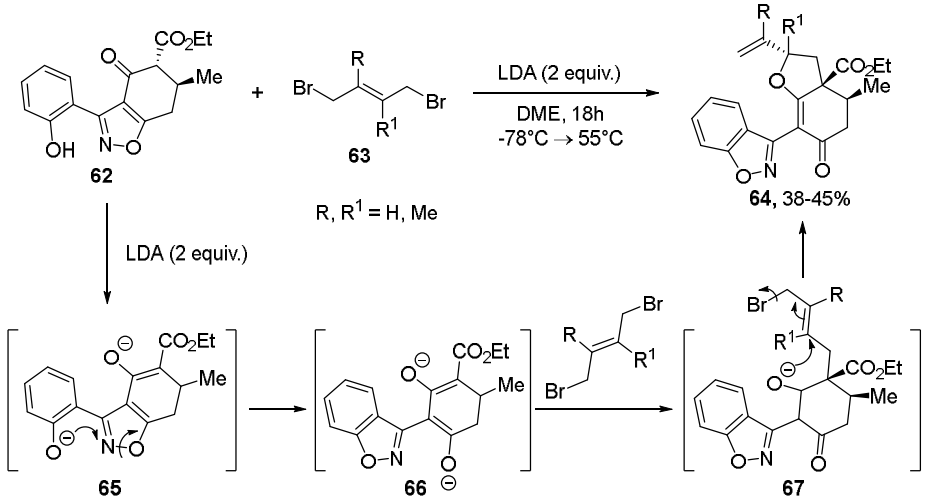
Scheme 11. Synthesis of benzisoxazole **59** *via* cyclization of oxime **56**.

Cyclization of hydroxyaryl oximes can be successfully performed with sulfonic anhydrides and sulfonyl chlorides. The common procedures include the use of triethylamine with TsCl,[44,66] MsCl, or $SOCl_2$.[13,67] The reaction of hydroxyaryl oximes with triflic anhydride (Tf_2O) was suitable for the efficient synthesis of benzisoxazoles and quinolone-fused isoxazoles.[68] In particular, this approach was used for the synthesis of potent dual PPAR α/γ agonist **3** (Scheme 12).[13] Thus, benzisoxazole **61** was formed in high yields (up to 90%) by the action of either MsCl or $SOCl_2$ upon oxime **60**. Further Bargellini reaction produced target α-aryloxyisobutyric acid derivative **3** in up to 95% isolated yield. Authors also demonstrated that this reaction can be performed on kilogram scale.[13]



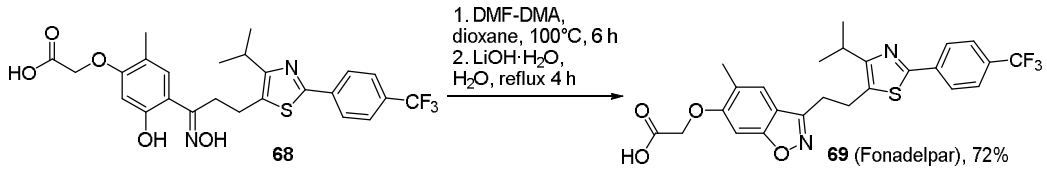
Scheme 12. Synthesis of benzisoxazoles **61** and its conversion into PPAR α/γ agonist **3**.

Leaving group on nitrogen atom can be rather complex and can be tethered to oxime carbon atom. In this case, the cyclization leads to the formation of benzisoxazole derivatives with carbon chain or carbocycle at the C-3. This interesting reaction was demonstrated by Suzuki *et al.* in the transformation of cyclohexane-fused isoxazole to benzisoxazole.[69] Treatment of 3-(2-hydroxyphenyl)-isoxazole derivative **62** with LDA and allyl dibromides **63** led to tandem alkylation-cyclization (Scheme 13). One of the proposed mechanisms starts with the double deprotonation of substrate **62** with 2 equivalents of LDA and generation of dianion **65**. It undergoes base-induced cyclization with N–O bond cleavage to give benzisoxazole intermediate **66**. Then, alkylation with dibromide and subsequent S_N2 cyclization in **67** affords final substituted benzisoxazoles **64** as a single diastereomer. Employment of 1,4-dibromobut-2-yne as dibromide source allows to obtain allene-bearing derivatives. Although the reported yields are moderate, this transformation demonstrates the fundamental opportunity for the facile preparation of benzisoxazole core from 3-(2-hydroxyaryl)-isoxazoles.



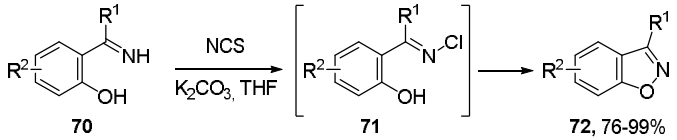
Scheme 13. Recyclization of isoxazole **62** to benzisoxazoles **64**.

Dimethylformamide-dimethylacetal (DMF-DMA) is another agent for the efficient cyclization of hydroxyaryl oximes.[70,71] In particular, it was applied for the conversion of aryloxime **68** into PPARδ agonist Fonadelpar **69**, that is used for the treatment of multiple sclerosis (Scheme 14).[71]



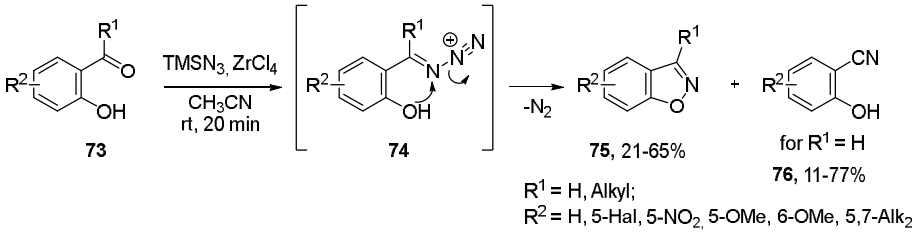
Scheme 14. Synthesis of Fonadelpar **69** from oxime **68**.

An alternative approach to benzisoxazole core *via* N–O bond formation is the synthesis from *o*-hydroxyaryl-*N*-haloimines. In 2011 Chen *et al.*[72] reported a new selective one-pot synthesis of benzisoxazoles from N-H ketimines **70**. For this purpose, imine is allowed to react with an halogenating reagent, such as NCS, leading to *in situ* formation of *N*-chloroimine **71**. Then substitution of chlorine at nitrogen atom occurs under basic conditions. Careful choice of reaction conditions (K_2CO_3 in THF) allowed to synthesize benzisoxazoles **72** selectively in excellent yields (Scheme 15). However, reaction of N-H imines **70** with 10% NaOCl (aq.) in isopropanol afforded isomeric benzo[*d*]oxazoles selectively (cf. Scheme 9). Later this approach was used for the synthesis of different biologically active benzisoxazole bearing molecules.[73,74]



Scheme 15. Synthesis of benzisixazoles **72** *via* chlorination of imines **70**.

In some cases, 1,2-benzisoxazoles can be prepared directly from 2-hydroxy benzoyl derivatives **73**. Usually it involves refluxing with hydroxylamine-*O*-sulfonic acid (H_2NOSO_3H)[75] or hydroxylamine.[76,77] An interesting example is the treatment of substrates **60** with trimethylsilyl azide in acetonitrile in the presence of $ZrCl_4$ (Scheme 16).[78] In this case, diazonium N_2^+ acts as a leaving group at nitrogen atom, and the title heterocycles are formed *via* dinitrogen extrusion from imine diazonium ion **74**. This approach allows the synthesis of benzisoxazoles **75** from salicylaldehydes **73** (R^1=H) in satisfactory yields, however formation of corresponding salicylonitriles **76** in significant amounts is observed. The authors also demonstrated that utilizing TfOH instead of $ZrCl_4$ in this reaction leads to selective formation of benzo[*d*]oxazoles.

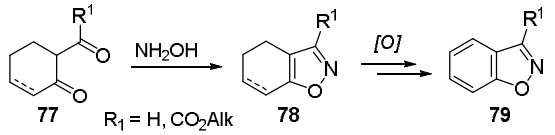


Scheme 16. Synthesis of benzisoxazoles **75** using $TMSN_3/ZrCl_4$ system,

2.3. Synthesis from cyclic 1,3-dicarbonyl compounds with further oxidation

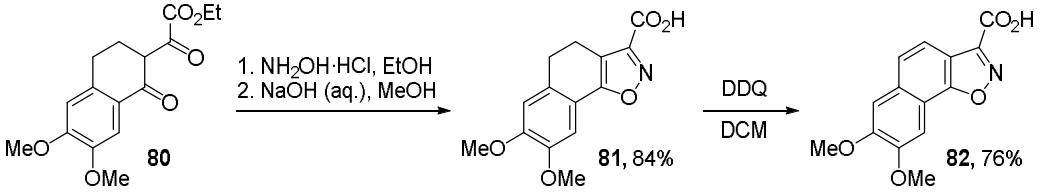
The preparation of 1,2-benzisoxazoles and naphthoisoxazoles can be accomplished through the oxidation of the corresponding saturated derivatives. Generally, the reaction of hydroxylamine with

1,3-dicarbonyl compounds **77** provides benzisoxazole derivatives **78** with dihydro- or tetrahydro- benzene fragment. Further C=C double bond(s) formation leads to the desired 1,2-benzisoxazoles **79** (Scheme 17). The advantage of this approach is the possibility to synthesize 3-unsubstituted 1,2-benzisoxazoles (R^1=H) or benzisoxazole-3-carboxylic acids (R^1=COOH, after saponification of corresponding esters), which could not be obtained *via* the base-promoted cyclization of oximes (see Scheme 8).



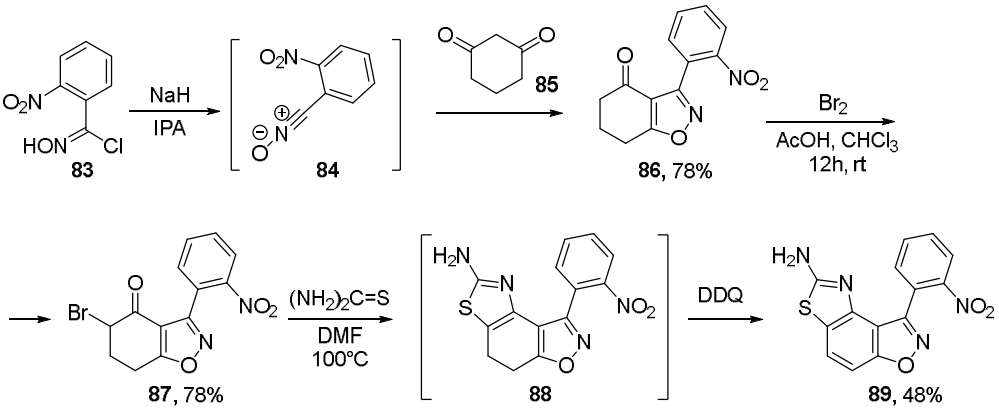
Scheme 17. General scheme for the synthesis of benzisoxazoles **79** *via* sequential oximation and oxidation of diketones **77**.

This protocol was used for the preparation of aryl substituted benzisoxazoles,[79,80] indoloisoxazoles,[81] and bioactive naphthoisoxazole-3-carboxylic acid derivatives.[82,83] As exemplified in Scheme 18, cyclocondensation of carbonyl compound **80** with hydroxylamine followed by saponification with aqueous NaOH gave dihydronaphthoisoxazole derivative **81**. Subsequent aromatization was carried out by oxidation with DDQ and smoothly afforded substituted naphthoisoxazole-3-carboxylic acid **82**.[83]



Scheme 18. Synthesis of benzisoxazole **82**.

Hydrogenated benzisoxazole derivatives can be synthesized by the base-promoted cyclocondensation of diketones and nitrile oxides.[84,85] For this purpose, chlorooxime **83** (hydroxymoyl chloride) was treated with a base (sodium hydride) to give nitrile oxide **84** *in situ*. Trapping this intermediate with cyclohexane-1,3-dione **85** results in the formation of hydrogenated benzisoxazole **86**. Further halogenation and cyclization of α-bromoketone **87** with thiourea, followed by aromatization of the resulting cyclohexadiene ring in **88** with DDQ, afforded 5-aminothiazolobenzisoxazole **89** in 48% yield (Scheme 19).[86]

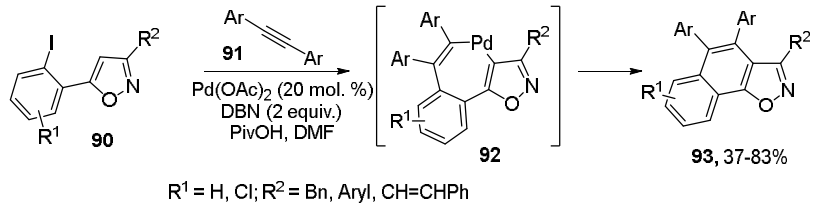


Scheme 19. Synthesis of benzisoxazole **89** *via* unsaturated derivatives **86-88**.

It is important to note that in the absence of DDQ a mixture of **88** and **89** (3:1) was obtained. Noteworthy, direct synthesis of benzisoxazole core *via* reaction of unsaturated 1,3-dicarbonyl compound **77** with hydroxylamine hydrochloride in alcoholic KOH in the absence of any oxidizing agent has been reported (Scheme 19).[87]

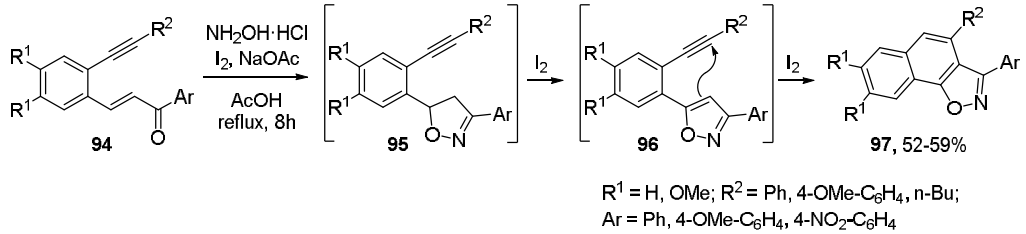
2.4. Benzene ring formation. Synthesis from substituted isoxazoles

Synthesis of benzisoxazole core can be performed not only by five-membered ring closure, but also by benzene fragment formation. This convenient approach includes annulation reactions of various substituted isoxazole derivatives. For instance, naphthalene-fused isoxazoles can be easily synthesized from 5-iodoaryl-substituted isoxazoles **90** and symmetrical alkynes **91** by palladium-catalyzed annulation.[88] The plausible reaction mechanism involves the insertion of alkyne and C–H activation of isoxazole core to give a 7-membered palladacycle intermediate **92**. Subsequent reductive elimination affords target naphtho[2,1-d]isoxazoles **93**. This transformation allows the preparation of products **91** possessing various substituents on both isoxazole and naphthalene nuclei (Scheme 20).



Scheme 20. Synthesis of benzisoxazole **93** *via* annulation of substrates **90** with alkynes.

Another approach to naphthoisoxazole synthesis is a two-step procedure based on *o*-alkynylarene chalcones.[89] When chalcones **94** were heated under reflux with hydroxylamine hydrochloride in the presence of iodine in AcOH, both oxidative cyclocondensation (**94→95→96**) and electrophilic hydroarylation took place in a tandem manner to give final naphthoisoxazoles **97** in good yields (Scheme 21). Thus, the reaction proceeded *via* 5-aryl isoxazole intermediate **96** that underwent iodine-mediated cyclization. Utilizing quinoline-based chalcones in this reaction opened access to more complex quinoline-fused benzisoxazoles (isoxazoloacridines).

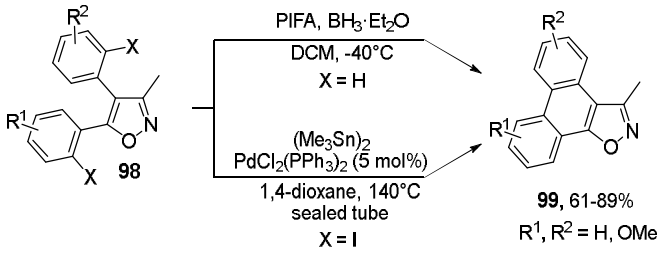


Scheme 21. Synthesis of naphthoisoxazoles **97** *via* oximation/iodine-mediated cyclization.

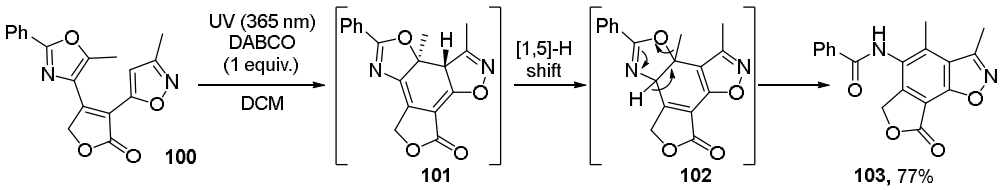
4,5-Diarylisoxazoles can be transformed into another type of polyarene-fused isoxazoles. Thus, cyclization of 4,5-bis(aryl) substituted isoxazoles **98** under oxidative conditions (PIFA and $BH_3 \cdot Et_2O$ in DCM, X=H)[90,91] or *via* palladium-catalyzed intramolecular biaryl coupling (heating with $(Me_3Sn)_2$ and $Pd(PPh)_3)_2Cl_2$ in 1,4-dioxane, X=I)[91,92] is a facile approach to phenanthro[9,10-d]isoxazoles **99** (Scheme 22).

Recently, a new general procedure for the synthesis of benzannulated heterocycles was reported.[93] This approach includes photocyclization of 1,2-dihetarylethenes and can be used as a tool for the benzannulation of heterocycles. A large array of dihetarylethenes was used to produce a broad scope of various benzo-fused heterocycles such as quinolones, isoquinolones, benzothiophenes and others. Among them, the successful preparation of 1,2-benisoxazole was demonstrated. In particular, irradiation of isoxazole-bearing dihetarylethene **100** with a long-wave UV light (365 nm) led to benzene ring formation of

benzisoxazole core by sequential [1,5]-H shift in photogenerated intermediate **101** and aromatization of **102**, ultimately producing highly functionalized benzisoxazole **103** in good yield (Scheme 23).

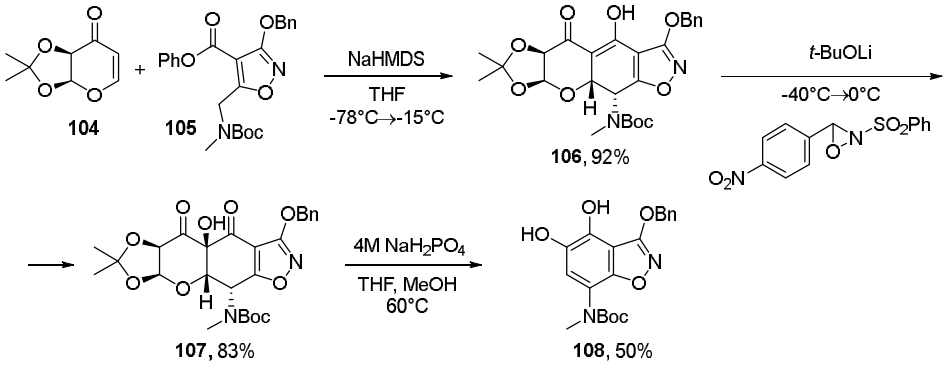


Scheme 22. Synthesis of benzisoxazoles **99** from diarylisoxazoles **98**.



Scheme 23. Photocyclization of substrate **100** for the synthesis of benzisoxazole **103**.

Constructing of benzene ring on a preformed isoxazole scaffold allows to set new various substituents in the target benzisoxazole core. This approach was applied for the synthesis of polyhydroxy substituted derivatives.[94,95] For example, cyclization of isoxazole derivative **105** with protected pyrone **104** under basic conditions afforded polycyclic product **106**. Further oxidation with Davis oxaziridine reagent and fragmentation of **107** upon treatment with monosodium phosphate solution led to 4,5-dihydroxybenzisoxazole derivative **108**, although the yield was moderate (Scheme 24).[94]



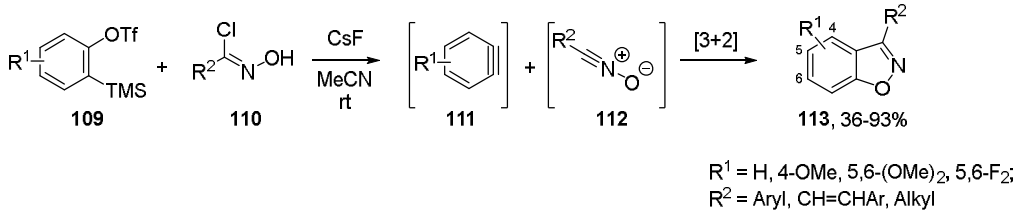
Scheme 24. Synthesis of benzisoxazole **108** from isoxazole **105**.

2.5. Synthesis *via* [3+2]-cycloaddition reactions. Formation of C–C and C–O bonds

2.5.1. An aryne-based route

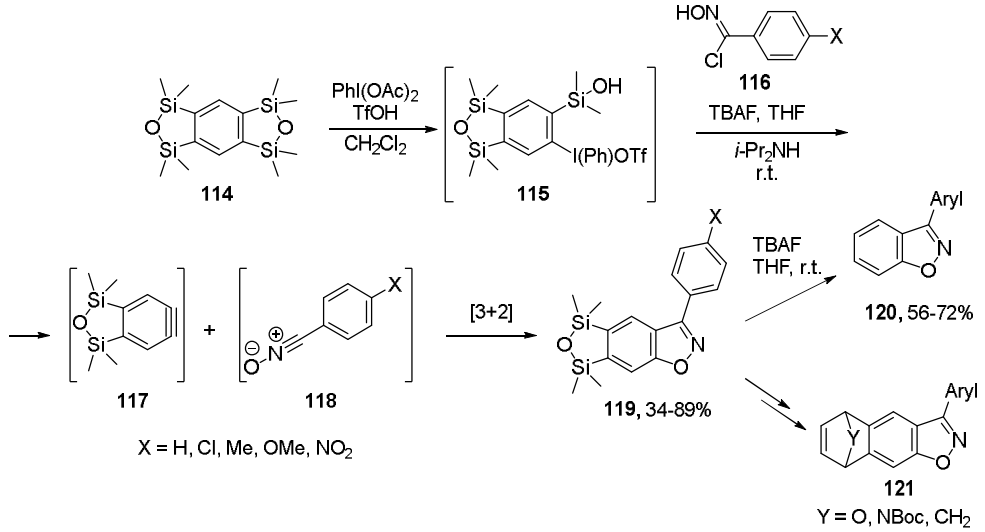
In the last 20 years, cycloaddition reactions of high reactive aryne intermediates with various 1,3-dipoles became an efficient method for the synthesis of benzo-fused heterocycles,[96] and particularly, 1,2-benzisoxazoles.[97] Until 2009, only a few examples of benzisoxazole synthesis from arynes had been reported and the yields were quite moderate.[18] The real "rebirth" of an aryne-based methodology for benzisoxazole preparation occurred when convenient and bench-stable aryne precursors, such as *o*-silylaryl

triflates **109** (Kobayashi aryne precursors), were introduced in organic synthesis. Silylaryl triflates **109** and hydroxymoyl chlorides **110** were treated with fluoride source to give highly reactive aryne **111** and nitrile oxides **112** *in situ*. Excess of fluoride ion was needed because it induced generation of aryne and also acted as a base for nitrile oxide formation (Scheme 25). Thus, slow addition of hydroxymoyl chlorides **110** to aryne precursors **109** in the presence of 6 equiv. CsF in acetonitrile at room temperature allowed obtaining a variety of substituted benzisoxazoles **113** in high yields and with satisfactory regioselectivity (for unsymmetrically substituted arynes, $R^1 \neq H$).[98] The same reaction can be effectively performed with TBAF in THF instead of CsF.[99,100]



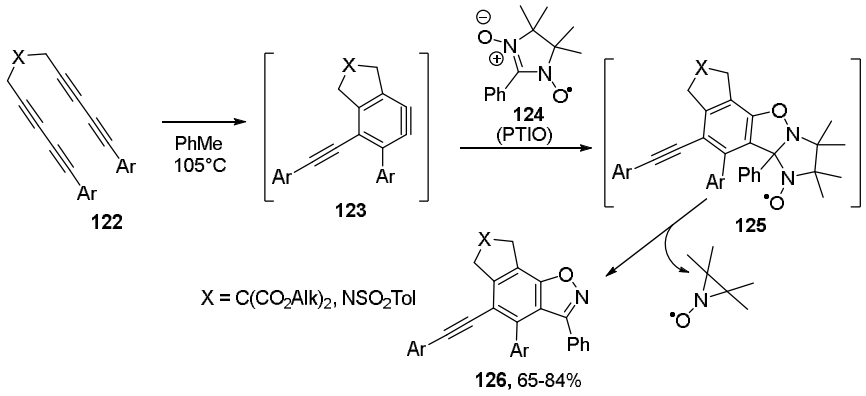
Scheme 25. Synthesis of benzisoxazoles **113** by cycloaddition of nitrile oxides **112** with arynes **111**.

Various silylaryl triflates[101-103] were widely used as starting materials for the preparation of benzisoxazoles, however, studies of different aryne precursors have been carried out. Numerous arynes precursors such as *o*-(trimethylsilyl)phenyl trimethylsilyl ethers,[104] arylboronic acids,[105-113] iodophenyl triflates[114-120] or anthranilic acid[121] were successfully applied for the synthesis of benzisoxazoles. An interesting example includes benzisoxazole synthesis from benzobis(oxadisilole) **114** and hydroxymoyl chlorides **116**.[122] Consecutive treatment of **114** with $PhI(OAc)_2$ and TBAF in THF afforded oxadisilole-fused benzyne **117** *via* iodonium salt **115**. It then that reacted with *in situ* generated nitrile oxide **118** to give corresponding oxadisilole-fused 3-aryl benzisoxazoles **119** in high yields (Scheme 26). Oxadisilole fragment can be removed by treatment with TBAF to give 3-aryl-benzisoxazoles **120**. Also **119** can be considered as new aryne precursor and transformed into benzisoxazole derivatives **121** by trapping with various 1,3-dienes.



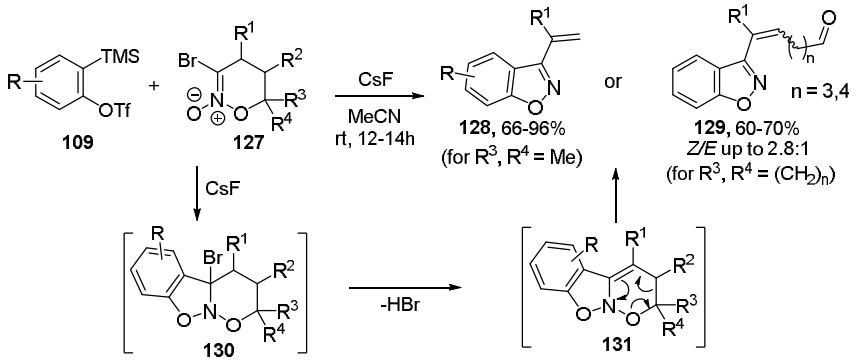
Scheme 26. An aryne-based synthesis of benzisoxazoles starting from oxadisilole **114**.

Although nitrile oxides are the most common reactants for the preparation of benzisoxazoles from arynes, other 1,3-dipoles were used. Recently, an interesting cycloaddition of nitrone **124** containing *N*-oxile fragment (PTIO, 2-phenyl-4,4,5,5-tetramethylimidazoline-3-oxide-1-oxyl) with arynes generated from different types of precursors was reported.[123] When tetrayne precursor **122** in toluene was used, hexadehydro-Diels-Alder reaction proceeded to give alkynyl-substituted aryne intermediate **123**. Trapping with PTIO and further fragmentation of benzisoxazoline intermediate **125** resulted in the formation of functionalized 3-phenyl benzisoxazoles **126** in good yields (Scheme 27). Reaction of PTIO with Kobayashi aryne precursor and CsF in acetonitrile also led to 3-phenyl benzisoxazoles.[123]



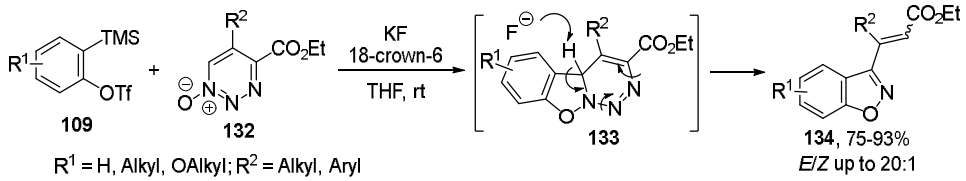
Scheme 27. Synthesis of benzisoxazoles **126** from arynes and *N*-oxide **124**.

In our research group, different types of 1,3-dipoles, rather than nitrones, have been used. Variously substituted six-membered cyclic nitronates (5,6-dihydro-4*H*-1,2-oxazine *N*-oxides) were studied in reactions with *in situ* generated arynes. Thus, coupling of 3-bromonitronates **127** with silylaryl triflates **109** afforded a wide scope of 3-vinylbenzisoxazoles **128**, **129** in high yields and excellent regioselectivity (for R≠H) (Scheme 28).[124] In this reaction 3-halosubstituted 1,2-oxazine *N*-oxides can be considered as surrogates for unsaturated nitrile oxides that undergo further [3+2]-cycloaddition (cf. Scheme 25). The proposed mechanism starts with the formation of halogenated nitroso acetal **130** and elimination of HBr to give the key intermediate **131**. [4+2]-Cyclofragmentation of the 5,6-dihydro-2*H*-1,2-oxazine ring in **131** leads to vinylbenzisoxazoles **128** and carbonyl compound (acetone, in case R^3=R^4=CH_3). Utilizing cycloalkane-annulated substrate (R^2–R^3=-$(CH_2)_n$-) allowed to tether the formed carbonyl function and afforded vinylbenzisoxazoles **129** with a pendant aldehydic moiety.



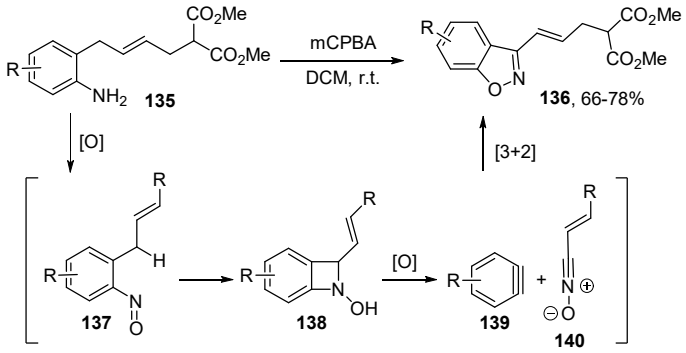
Scheme 28. Synthesis of benzisoxazoles **128**, **129** by tandem cycloaddition/cycloreversion of nitronates **127**.

Recently, benzisoxazole synthesis was performed *via* reaction of 1,2,3-triazine 1-oxides **132** with aryne precursors **109**.[125] In this reaction, the initially formed cycloadduct **133** does not remain intact and undergoes cyclofragmentation with extrusion of N_2 to form 3-alkenyl benzisoxazoles **134** in high yields and diastereoselectivity (Scheme 29).



Scheme 29. Synthesis of benzisoxazoles **134** from triazine 1-oxides **132**.

An interesting benzisoxazole formation took place during the oxidation of substituted 2-allylanilines **135** with mCPBA in DCM.[126] The plausible mechanism of this transformation is shown in Scheme 30. In the first step, the free amine fragment was converted into nitroso compound **137**. Subsequent cyclization to azetidine intermediate **138** and its oxidation led to *in situ* formation of aryne **139** and nitrile oxide **140**. Further [3+2]-cyclization resulted in 3-vinylbenzisoxazoles **136** in good yields. Notably, the oxidation conditions did not affect the olefin functionality.



Scheme 30. Synthesis of benzisoxazoles **136** by oxidation of substrates **135**.

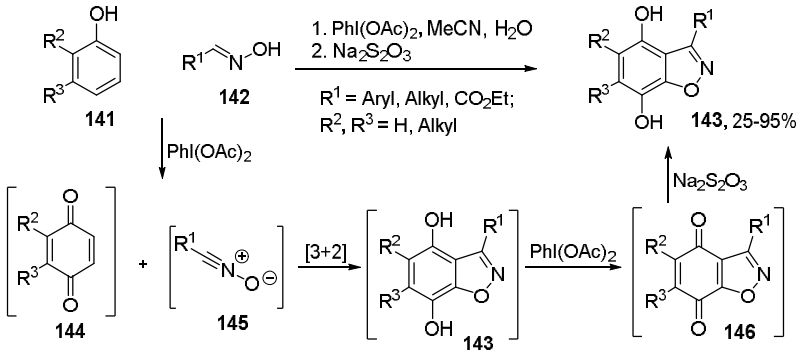
2.5.2. Nitrile oxide-benzoquinones cycloaddition

The cycloaddition reaction of nitrile oxides with benzoquinones is another common method for 1,2-benzisoxazole preparation.[127] An interesting one-pot synthesis of benzisoxazole-4,7-diols **143** in aqueous medium was reported.[128] Both highly reactive nitrile oxides **145** and 1,4-benzoquinones **144** were generated *in situ* from easily available oximes **142** and substituted phenols **141**, respectively, upon treatment with iodobenzene diacetate (Scheme 31). Further [3+2]-cycloaddition, oxidation with an excess of $PhI(OAc)_2$, and reduction of quinone **146** with sodium thiosulfate afforded various substituted benzisoxazole-4,7-diol derivatives **143** in yields up to 95%. Similar approaches based on nitrile oxides cycloaddition with masked benzoquinones were also successfully utilized.[129,130]

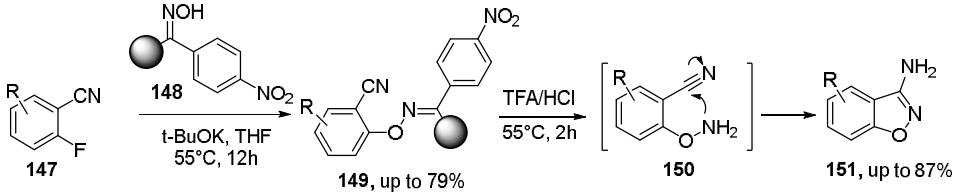
2.6. C=N double bond formation

Benzisoxazole synthesis *via* C=N double bond formation is mostly used for the preparation of 3-aminobenzisoxazoles. This approach is similar to the base-promoted ring closure (see chapter 2.1.), but with the reversed sequence of bond formation, namely C–O bond is formed in the first step, followed by C=N bond formation. The synthesis starts with the reaction of *o*-halogenated benzonitriles or *o*-halogenated benzophenones with an oxime source (acetone oxime,[131] Kaiser oxime resin,[132,133] or recyclable "fluorous oxime tag"[134]) to give the corresponding *O*-arylated oxime derivative *via* aromatic substitution. Further

acidic treatment produces the target benzisoxazole core through hydrolysis of oxime C=N double bond and cyclization of free NH_2 group to cyano fragment (for nitriles) or to C(O)Ar (for benzophenones). Treatment of *o*-halogenated benzonitriles with acetohydroxamic acid under basic conditions also leads to the desired 3-amino-benzisoxazoles in one step.[135,136] Thus, the reaction of 2-fluorobenzonitriles **147** with the base and Kaiser oxime resin **148** gave *O*-aryloximes **149**. Their subsequent treatment with TFA/HCl mixture afforded 3-amino-benzisoxazoles **151** by cyclization of hydroxylamines **150** in good yields (Scheme 32).[132,133]



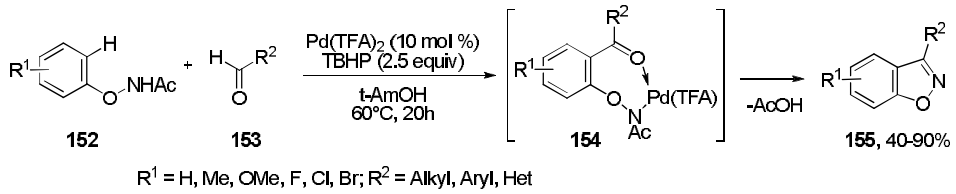
Scheme 31. Synthesis of benzisoxazoles **143** by cycloaddition of quinones **144**.



Scheme 32. Synthesis of 3-aminobenzisoxazoles **151** *via* cyclization of hydroxylamines **150**.

2.7. Miscellaneous methods

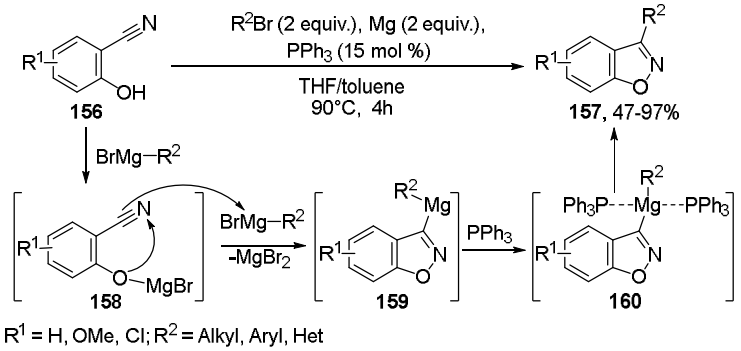
In addition to the five most common methods for 1,2-benzisoxazole core synthesis described above, some other approaches have also been reported. In 2014, palladium-catalyzed synthesis of benzisoxazole by formal intermolecular [4+1]-annulation was proposed.[137] Thus, the reaction of *N*-phenoxyacetamides **152** with various aldehydes **153** in the presence of 10 mol% $Pd(TFA)_2$ afforded the corresponding 3-substituted benzisoxazoles **155** *via* the proposed intermediate **154** in good yields (Scheme 33). The reaction was suitable for diverse substrates including aromatic, heterocyclic, and aliphatic aldehydes.



Scheme 33. Synthesis of benzisoxazoles **155** *via* coupling of hydroxamates **152** with aldehydes **153**.

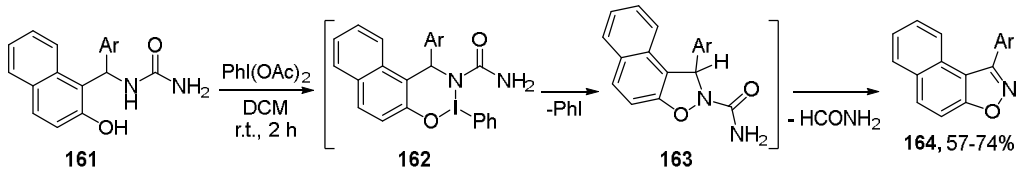
In 2017, Zhang *et al.* reported novel efficient one-pot PPh_3 promoted transformation of salicylonitriles **156** and various bromides into 3-aryl and 3-alkyl 1,2-benzisoxazoles (Scheme 34).[138] In this protocol, a Barbier-Grignard-type reaction was used to construct a C–R^2 bond and the heterocycle ring in one step. The authors proposed an attack of oxygen atom in intermediate **158** at the nitrogen atom of the cyano group to

provide a carbanion, which reacts with the second equivalent of Grignard reagent to generate intermediate **159**. Further interaction with PPh_3 and reductive elimination from intermediate **160** produces the target benzisoxazoles **157** in high yields. Both alkyl and aryl bromides can be used in this approach.



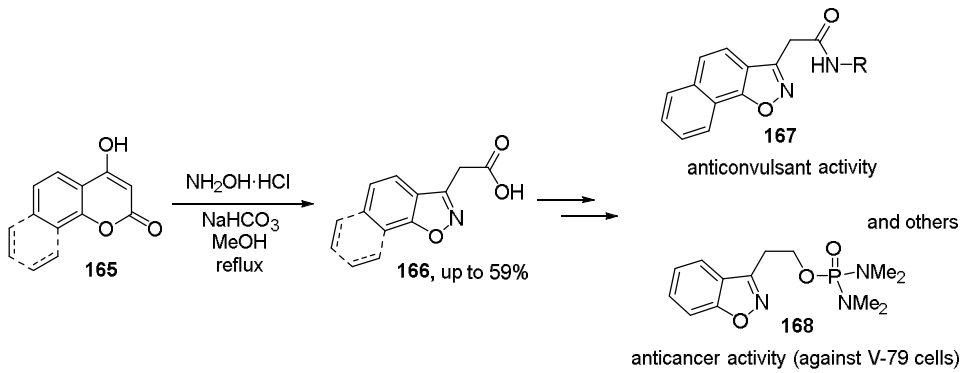
Scheme 34. Synthesis of benzisoxazoles **157** by cyclization of salicylonitriles **156**.

Unusual synthesis of naphtho[1,2-d]isoxazoles by oxidation of 1-amidoalkyl-2-naphthols **161** with $PhI(OAc)_2$ has been reported.[139] This reaction includes formation of six-membered cyclic intermediate **162**, which undergoes reductive elimination of iodobenzene with the N–O bond formation. Aromatization of corresponding naphthoisoxazoline intermediate **163** (*via* elimination of the formamide) affords the target 3-aryl naphthoisoxazoles **164** in good yields (Scheme 35).



Scheme 35. Synthesis of benzisoxazoles **164** by oxidative cyclization of naphthols **161**.

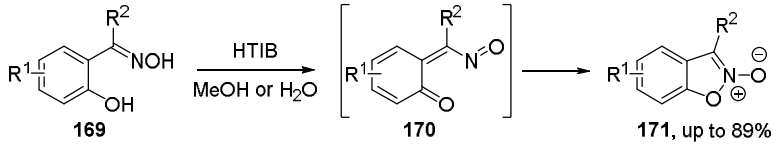
The reaction of hydroxylamine with 4-hydroxycoumarines **165** is a facile method for the synthesis of benzisoxazole-3-acetic acids **166**. Further transformations can give various 3-substituted derivatives (*e.g.* naphthoisoxazole derivatives **167** or benzisoxazole phosphorodiamidates **168**) with promising biological activity (Scheme 36).[140,141]



Scheme 36. Synthesis of benzisoxazole-acetic acids **166** from coumarines **165**.

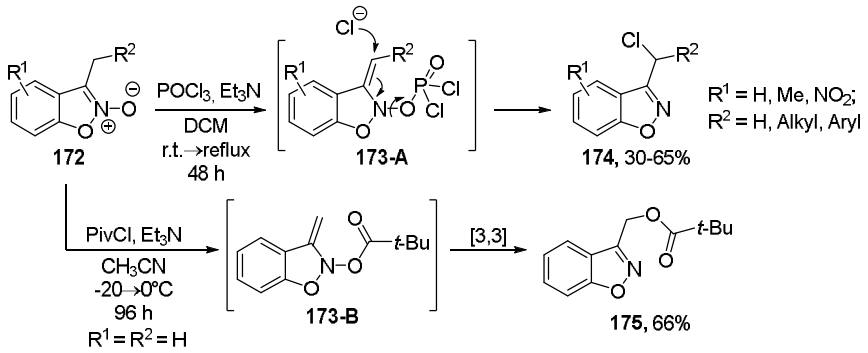
2.8. Synthesis of benzisoxazole *N*-oxides and their rearrangements

1,2-Benzisoxazole *N*-oxides cannot be synthesized by direct oxidation of the preformed 1,2-benzisoxazole core.[18] However, an efficient preparation of these compounds can be effected by an alternative approach, oxidative cyclization of 2-hydroxyaryl ketoximes **169** ($R^2 \neq H$) with various oxidizing agents [such as $PhI(OAc)_2$,[142] lead tetraacetate ($Pb(OAc)_4$),[57,143] sodium perborate ($NaBO_3$),[144] Koser's reagent ([hydroxy(tosyloxy)iodo]benzene or HTIB),[145,146] NaOCl,[147,148] AgO/NMMO,[47,149] or *N*-chlorosuccinimide].[150] The reaction involves oxidation of starting oxime to give the nitroso quinone methide intermediate **170**. Its further cyclization produces 3-alkyl- and 3-aryl substituted benzisoxazole *N*-oxide derivatives **171** (Scheme 37).



Scheme 37. Synthesis of benzisoxazole *N*-oxides **171** by oxidation of oximes **169**.

Benzisoxazole *N*-oxides can be used as precursors for other benzisoxazole derivatives. Thus 3-chloromethyl-benzisoxazoles can be effectively prepared *via* Boekelheide rearrangement of benzisoxazole *N*-oxides.[147] For this purpose, treatment of the corresponding 3-alkylbenzisoxazole *N*-oxides **172** with $POCl_3$ in the presence of base gives good yields of 3-chloromethyl substituted benzisoxazole derivatives **174** *via* rearrangement of *N,N*-bisoxyenamine intermediate **173-A** (Scheme 38). In a similar fashion, acylation of benzisoxazole *N*-oxide was followed by *in situ* [3,3]-rearrangement of **173-B** leading to product **175**.[151]

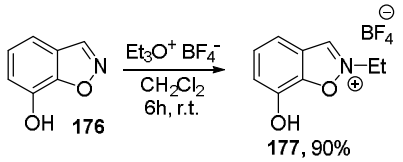


Scheme 38. Functionalization of benzisoxazole *N*-oxides **172** using [3,3]-rearrangement of bisoxyenamines.

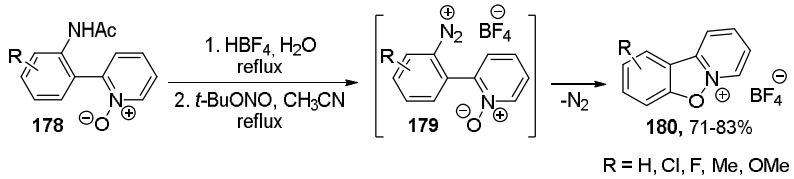
3. Benzisoxazolium salts

As typical for amine derivatives, nitrogen atom in benzisoxazoles can be quaternized to give 1,2-benzisoxazolium salts. These compounds can be prepared by several approaches. The most common method is a direct quaternization of nitrogen atom in preformed benzisoxazole core with various alkylating agents. Usually dimethyl sulfate[152] and trialkyloxonium tetrafluoroborate[153] are applied for this reaction (Scheme 39). Thus, treatment of benzisoxazole **176** with $Et_3O^+BF_4^-$ in DCM afforded ethyl benzisoxazolium salt **177** in 90% yield. Further anion exchange can be also performed for the synthesis of the specific benzisoxazolium salts.[152]

For the preparation of benzo-fused benzisoxazolium salts **180** (*e.g.* benzisoxazolo[2,3-a]pyridinium[154] and benzisoxazolo[2,3b]isoquinolinium[155] salts) another approach was used. It involved the diazotization of substrates **178** and the cyclization of the *in situ* formed pyridine *N*-oxides **179** possessing diazonium moiety (Scheme 40). Intramolecular substitution of N_2 furnished products **180**.

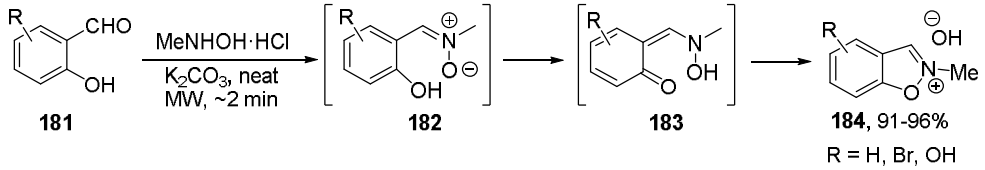


Scheme 39. *N*-Methylation of benzisoxazole **176**.



Scheme 40. Synthesis of annulated benzisoxazolium salts **180**.

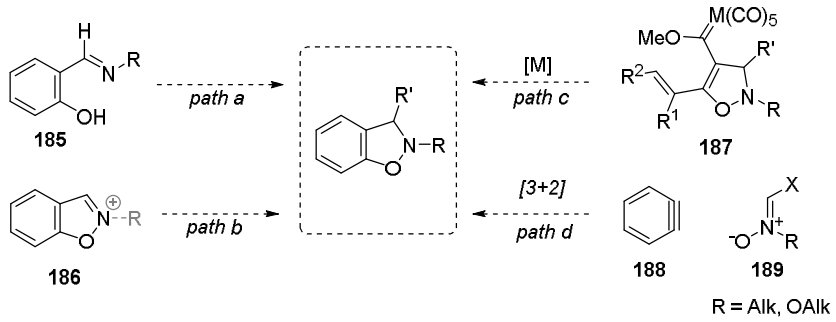
For the synthesis of benzisoxazolium hydroxides an efficient one-pot microwave-assisted procedure has been suggested.[156] MW irradiation of a mixture of salicylaldehydes **181**, *N*-methylhydroxylamine hydrochloride, and K_2CO_3 was reported to give *N*-methyl benzisoxazolium hydroxides **184** in excellent yields (Scheme 41). The authors proposed that the process involved initial formation of nitrone **182**, its tautomerization and cyclization of *N*-hydroxyenamine **183**. Reaction with *N*-phenylhydroxylamine did not provide the desired *N*-phenyl benzisoxazolium salt. Although this approach looks promising, there were no other reports about utilizing this reaction.



Scheme 41. Synthesis of benzisoxazolium salts **184**.

4. Synthesis of 2,3-dihydro-1,2-benzisoxazoles (benzisoxazolines)

2,3-Dihydro-1,2-benzisoxazoles (1,2-benzisoxazolines) are the partly hydrogenated benzisoxazole derivatives. In general, these compounds cannot be prepared by direct hydrogenation of benzisoxazoles thus requiring alternative approaches. Reasonably, most of the existing approaches resemble those used for benzisoxazole formation (see Scheme 1). Common methods include cyclization of Schiff bases **185** (N–O bond formation, *path a*, Scheme 42), or transformation of preexisting benzisoxazole core **186** (*path b*).

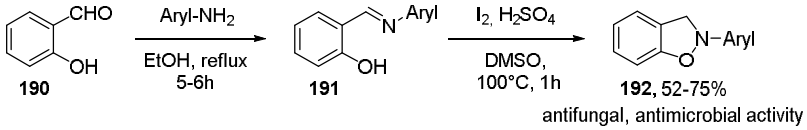


Scheme 42. General methods for 1,2-benzisoxazoline synthesis.

Another useful approach is based on direct benzene ring formation utilizing Fischer-type carbenes **187** (*path c*). Nevertheless, nowadays cycloaddition reactions of arynes **188** with dipoles **189** (*path d*) are the most common approach for 1,2-benzisoxazolines preparation (Scheme 42).

4.1. Synthesis from Schiff bases

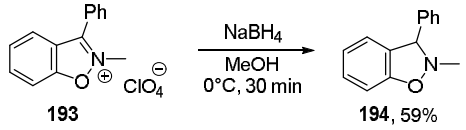
An interesting and facile 1,2-benzisoxazoline synthesis was reported by the Sareen research group.[16,157,158] The reaction of salicylic aldehyde **190** with various anilines gave corresponding 2-hydroxyphenyl imines **191** (Scheme 43). Further cyclization of Schiff bases **191** with DMSO-I_2-H_2SO_4 afforded a wide scope of *N*-substituted 1,2-benzisoxazolines **192** possessing antifungal and antimicrobial activity.



Scheme 43. Synthesis of benzisoxazolines **192** *via* imines **191**.

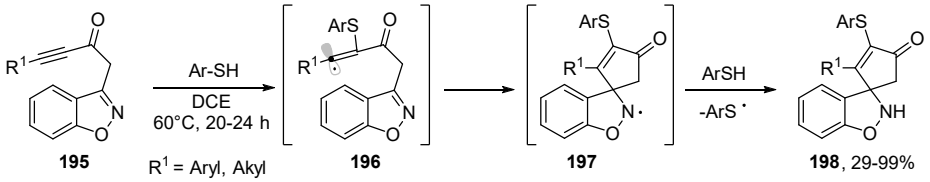
4.2. Synthesis from 1,2-benzisoxazoles

Although 1,2-benzisoxazolines cannot be obtained by direct reduction of the corresponding 1,2-benzisoxazoles,[18] *N*-alkyl-1,2-benzisoxazolium salts **193** can be successfully reduced to the corresponding 1,2-benzisoxazolines **194** upon treatment with sodium borohydride in methanol (Scheme 44).[152]



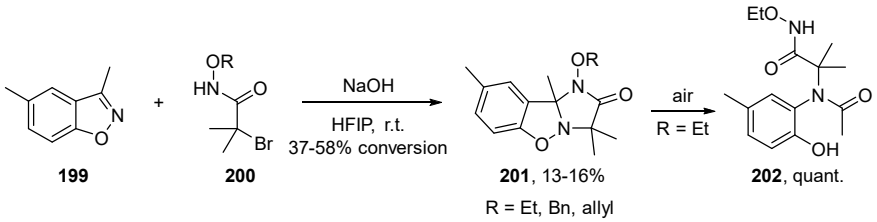
Scheme 44. Reduction of benzisoxazolium salt **193**.

Benzisoxazoles can be converted into benzisoxazolines through alternative approaches rather than reduction. An efficient method is based on radical dearomatizing spirocyclization of benzisoxazole tethered ynones **195**. The reaction proceeded through sequential addition of thiol-based radical to triple bond (**195→196**) and attack of the resulted vinyl radical to C=N double bond (**196→197**) yielding spirocyclic benzisoxazolines **198** (Scheme 45). The best results were achieved for electron rich aromatic thiols. Aliphatic thiols afforded the corresponding products only in trace amounts.[159]



Scheme 45. Thiyl radical mediated cyclization of benzisoxazoles **195**.

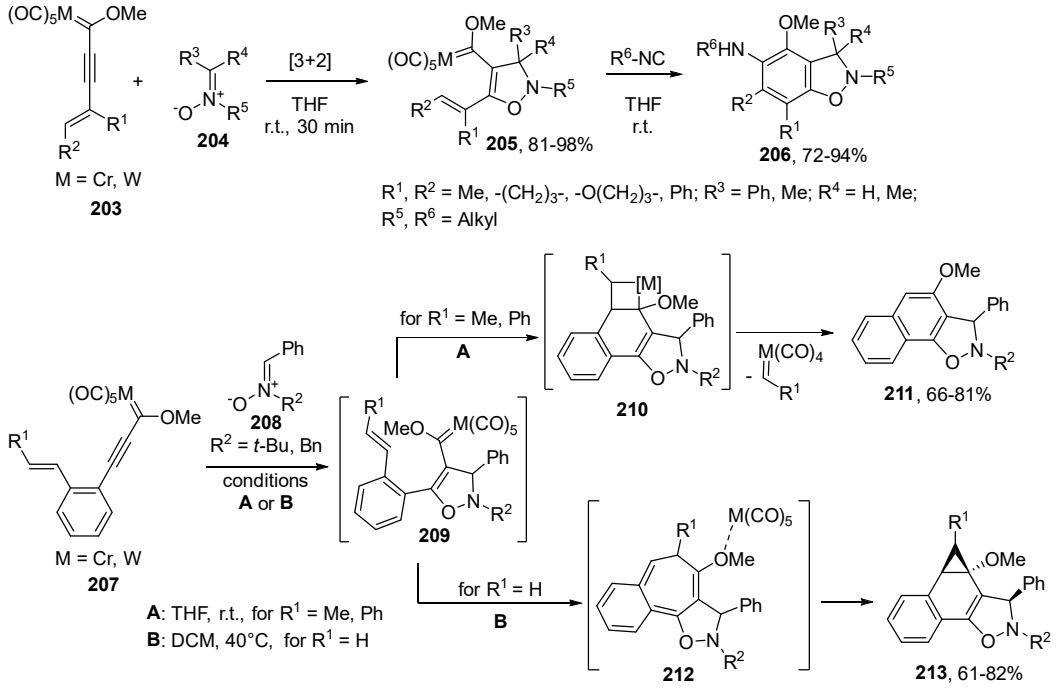
The reaction of 3,5-dimethylbenzisoxazole **199** with azaoxyallyl cations generated from α-halo hydroxamates **200** in hexafluoroisopropanol (HFIP) led to the formation of 1,2-benzisoxazolines **201**. However, low conversion and yield were reported (Scheme 46).[160] Furthermore, products **201** turned out to be unstable and could easily be converted to the amide **202** upon exposure to air.



Scheme 46. Synthesis and ring opening of benzisoxazolines **201**.

4.3. Benzene ring formation

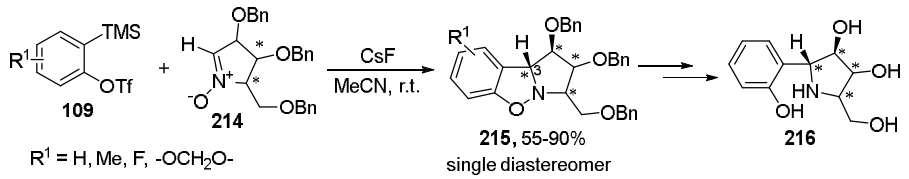
Formation of benzene ring on preformed isoxazoline moiety allows to synthesize densely substituted benzisoxazoline derivatives. Barluenga *et al.* carried out the synthesis of highly functionalized 1,2-benzisoxazolines by reaction of stable Fischer dienyl carbenes and isocyanides. Thus, chromium and tungsten carbenes **205** were prepared by regioselective [3+2]-cycloaddition of alkenylethynyl carbene complexes **203** with nitrones **204**. Treatment with two equivalents of an isocyanide R^6NC led to the annulation and afforded desired 5-amino substituted benzisoxazolines **206** (Scheme 47).[161] This reaction can be accomplished in a one-pot fashion, although the stepwise procedure usually gave higher yields. Later, this approach was modified for the one-pot synthesis of 2,3-dihydronaphtho[2,1-d]isoxazoles **211** from corresponding styrene-bearing Fischer carbenes **207**. In this case, the [3+2]-cycloaddition reaction of starting carbene **207** with nitrone **208** produced isoxazoline-substituted carbenes **209**. When $R^1 \neq H$, intramolecular metathesis occured **209**→**210**→**211** to give naphtho-fused isoxazolines **211**. However, reaction of starting carbene containing terminal double bond (R^1=H) led to the cyclopropanation product **213** through intermediate **212**, instead of the desired metathesis product formation.[162]



Scheme 47. Benzisoxazoline synthesis using Fischer carbenes **203**, and **207**.

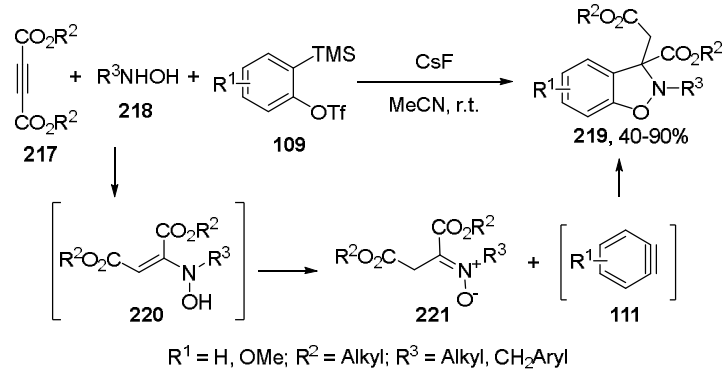
4.4. Aryne-based methodology

Similar to 1,2-benzisoxazoles synthesis, the most facile method for constructing 1,2-benzisoxazolines is based on aryne [3+2]-cycloaddition reactions with 1,3-dipoles. The classical approach includes reactions of nitrones with *in situ* generated arynes. There were few early examples of this type of cycloaddition in the works of Hajos[163] and Danishefsky.[164] This process was studied more thoroughly in 2010s.[165,166] Cycloaddition of nitrones with arynes generated from various precursors is presented in many works,[105-112,114-120,167] however silylaryl triflates **109** are mostly used in the aryne-based approach to benzisoxazolines. One of the most interesting examples included the coupling of chiral sugar-derived cyclic nitrones.[168] Reaction of the pentose-based nitrones **214** with Kobayashi aryne precursors **109** and CsF as fluoride source led to highly diastereoselective cycloaddition providing polysubstituted benzisoxazolines **215** as single diastereomers with *cis*-arrangement of hydrogen atom at C-3 and neighboring OBn group (Scheme 48). Further reductive N-O bond cleavage and removal of protecting groups allowed to synthesize aza-*C*-aryl glycosides **216**.



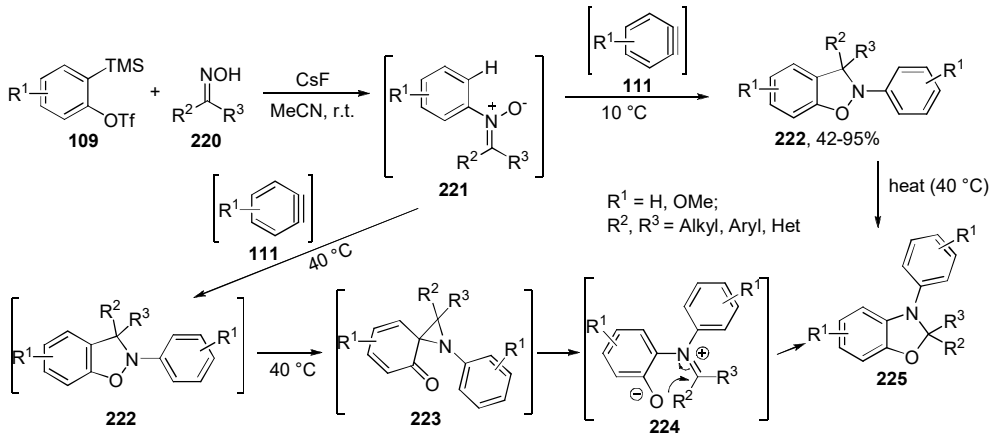
Scheme 48. Synthesis of carbohydrate-derived benzisoxazolines **215**.

The preparation of benzisoxazolines can be performed from *in situ* generated nitrones as well. Thus, a one-pot synthesis based on reaction of hydroxylamines and electron-poor alkynes with arynes was successfully accomplished.[169] Addition of various hydroxylamines **218** to acetylene dicarboxylates **217** afforded nitrones **221** through the formation of *N*-hydroxy-enamine intermediate **220** and tautomerization. [3+2]-Cycloaddition with aryne **111**, generated from **109**, gave functionalized benzisoxazolines **219** in good yields (Scheme 49).



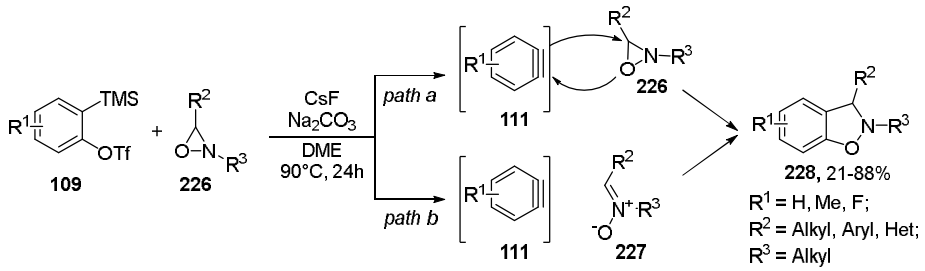
Scheme 49. Synthesis of benzisoxazolines **219** using *in situ* generated nitrones **221**.

Another unusual procedure for the synthesis of benzisoxazolines by *in situ* nitrone formation was reported by Yao *et al*.[170] The reaction involved *in situ* generation of ketonitrones **221** and arynes **111**, generated from ketoximes **220** and precursors **109**, respectively. Subsequent [3+2]-cycloaddition with a second equivalent of aryne at low temperature produced *N*-arylated benzisoxazolines **222**. However, when the reaction was performed at a higher temperature (40 °C), dihydrobenzo[d]oxazoles **225** were formed selectively. Heating benzisoxazolines **222** also leads to dihydrobenzo[d]oxazoles through thermal rearrangement *via* intermediates **223** and **224** (Scheme 50).



Scheme 50. Tandem arylation/cycloaddition of oximes **220** with arynes.

Oxaziridines are isomers of nitrones and may show similar behavior in cycloaddition reactions. Larock *et al* reported the highly efficient approach for the synthesis of dihydrobenzisoxazoles by the [3+2]-cycloaddition of *in situ* generated arynes and oxaziridines.[171] Thus, the reaction of *o*-(trimethylsilyl)aryl triflates **109** and oxaziridines **226** upon treatment with CsF afforded the desired benzisoxazolines **228** with a variety of substituents (Scheme 51). Two possible mechanisms can be proposed for product formation. In the first case (*path a*), insertion of an aryne **111** into the C–O bond of the oxaziridine ring occurs by a concerted mechanism. Another possible mechanism involves *in situ* formation of nitrone **227** *via* C–O bond cleavage in oxaziridine (*path b*) and subsequent cycloaddition.



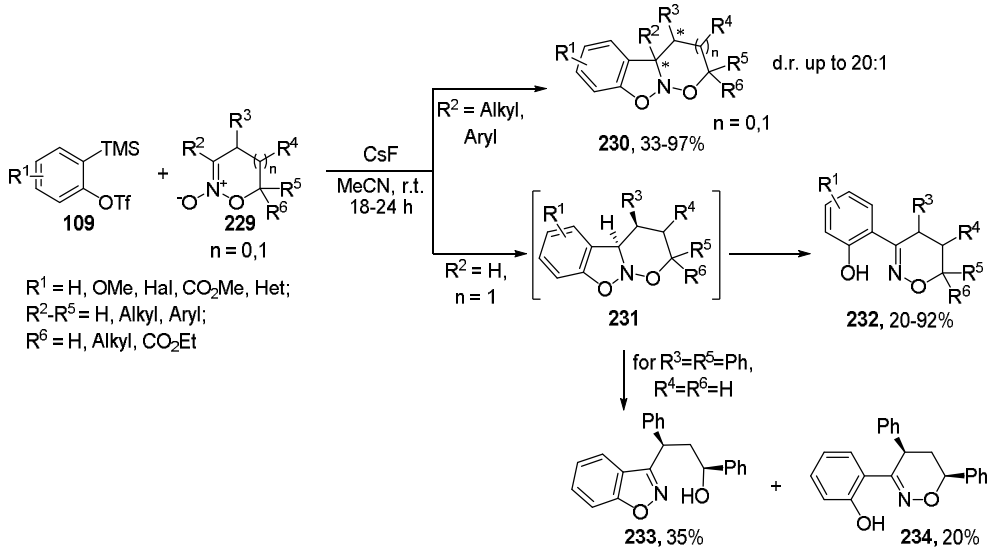
Scheme 51. Synthesis of benzisoxazolines from oxaziridines **226** and arynes.

Our research group proposed a new type of 1,3-dipoles for the synthesis of 1,2-benzisoxazolines from arynes.[172] Reaction of arynes, generated *in situ* from the corresponding aryl triflates **109**, was performed with five- and six-membered cyclic nitronates **229** to give tricyclic benzene-fused nitroso acetals **230** in high yields and complete diastereoselectivity (Scheme 52). It is worth noting that when 3-H-substituted 6-membered substrates **229** (R^2=H, n=1) were reacted with an aryne, primary cycloadducts **231** usually turned out to be unstable under reaction conditions and suffered N–O cleavage to form corresponding 3-aryl 1,2-oxazines **232**. In some cases, benzisoxazoles were formed as side products, as exemplified by the formation of products **233** and **234**.[173]

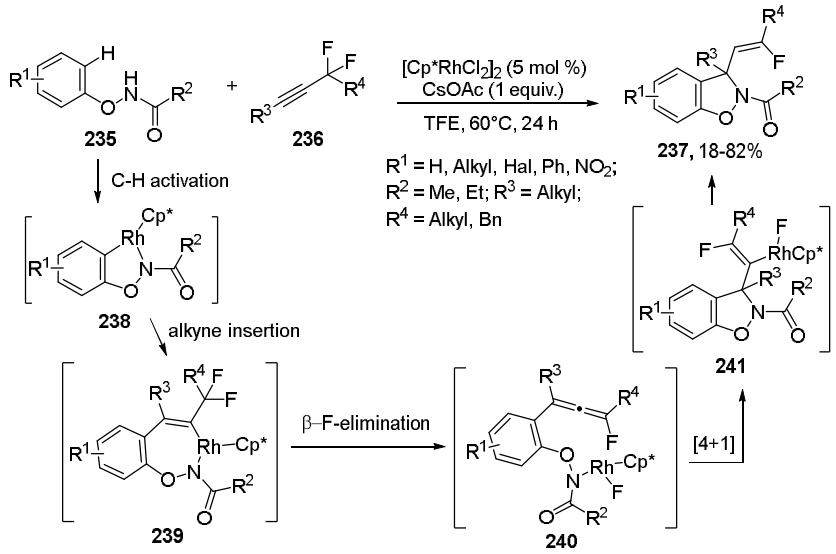
4.5. Rh-catalyzed cyclization

Rh-catalyzed [4+1]-annulations are widely used for the synthesis of various 5-membered heterocycles. However, to the best of our knowledge, a single example of constructing benzisoxazoline core has been reported so far.[174] Rh(III)-catalyzed redox-neutral [4+1]-annulation of *N*-phenoxy amides **235** with difluoromethylalkynes **236** was realized to give direct access to the monofluoroalkenyl benzisoxazolines **237**

(Scheme 53). This reaction involves tandem C−H activation **235**→**238**, alkyne insertion **238**→**239**, selective β-elimination of fluorine atom **239**→**240**, and [4+1]-annulation **240**→**241**, followed by protolysis of the C−Rh bond **241**→**237**.



Scheme 52. Synthesis of oxazine-annulated benzisoxazolines **230**, and **231** and their ring opening.

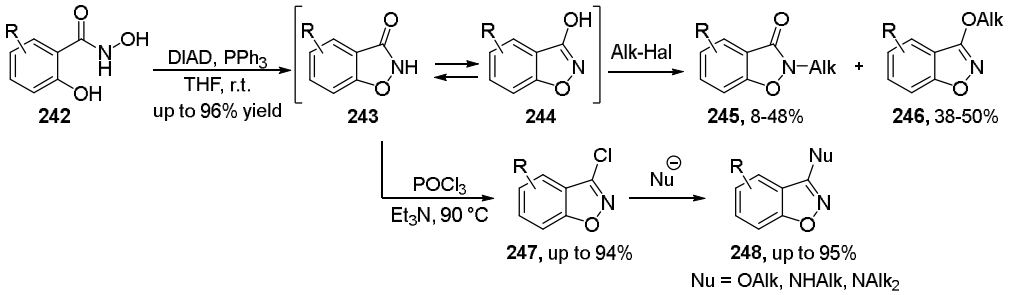


Scheme 53. Rh-catalyzed [4+1]-annulation of hydroxamates **235** with alkynes **236**.

5. 1,2-Benzisoxazoline-3-ones

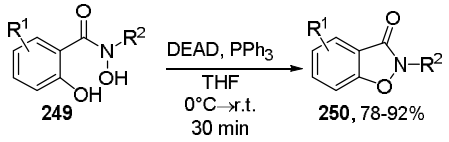
3-Hydroxy-1,2-benzisoxazoles **244** or its tautomeric form, 1,2-benzisoxazoline-3-ones **243**, display diverse biological activity making the synthesis of their derivatives an important task. For instance, *N*-alkylated 3-oxo-1,2-benzisoxazolines possess antioxidant and anticancer activity.[6,175] Synthetic methods

for the preparation of benzisoxazoline-3-ones are similar to the methods, described in the paragraphs 2.1., and 2.2: C–O and N–O bond formation, respectively. The most common approach for the synthesis of *N*-unsubstituted benzisoxazoline-3-ones involves cyclization of 2-hydroxyaryl hydroxamic acids **242** upon treatment with CDI,[176-182] DIAD/PPh_3,[183,184] $SOCl_2$[175] or NaOCl[185] (N–O bond formation) (cf. Schemes 10, 12). However, further direct alkylation gives both *N*- and *O*-alkylated products **245** and **246**[182] and cannot be used for the selective preparation of *N*-substituted derivatives (Scheme 54). Nevertheless, *N*-unsubstituted benzisoxazoline-3-ones **243** are used as precursors for the selective preparation of 3-chloro-1,2-benzisoxazoles **247**.[176,181] The latter can be transformed into benzisoxazoles **248** bearing alkoxy or amine functionality at C-3 position by nucleophilic substitution of chlorine atom.[186,187]



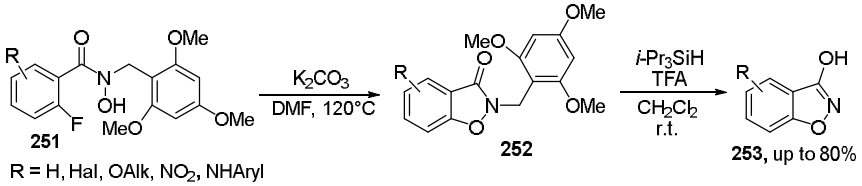
Scheme 54. Preparation and derivatization of benzisoxazolinones.

Clearly, for the efficient synthesis of *N*-substituted benzisoxazoline-3-ones, *N*-substituted hydroxamic acid derivatives should be used.[188,189] The first successful cyclization of *N*-alkyl and *N*-aryl hydroxamic acids **249** was performed by Shi with the use of Mitsunobu reagent (DEAD/PPh_3).[190] This reaction smoothly afforded various *N*-substituted 1,2-benzisoxazolin-3-ones **250** in high yields (Scheme 55). Moreover, this approach allowed minimizing side reactions such as the Lossen rearrangement, which led to the formation of isomeric benzoxazolinones.



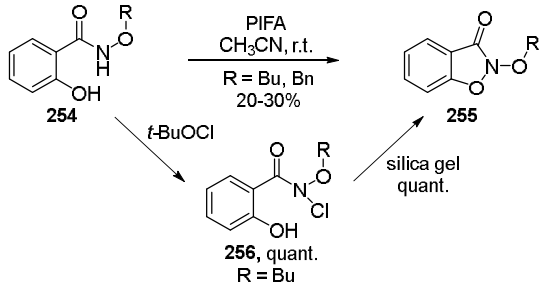
Scheme 55. Synthesis of *N*-substituted benzisoxazolinones **250** under Mitsunobu conditions.

Base-promoted ring closure of 2-haloaryl hydroxamic acids **251** is another useful method for the preparation of *N*-substituted benzisoxazoline-3-ones. Bases like K_2CO_3 in DMF[191,192] or aqueous KOH[193] can be applied for the cyclization step, similar to benzisoxazole synthesis from 2-haloaryl oximes (C–O bond formation, cf. Scheme 2). This reaction was used for the synthesis of *N*-trimethoxybenzyl derivatives **252**. Further cleavage of benzyl fragment upon treatment with triisopropyl silane and trifluoroacetic acid smoothly afforded the corresponding 3-hydroxy-1,2-benzisoxazoles **253** (Scheme 56).



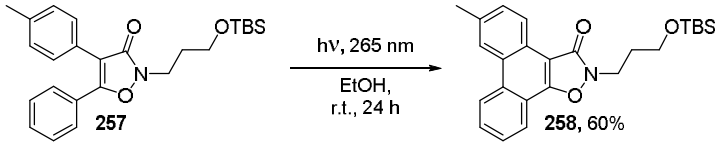
Scheme 56. Synthesis and debenzylation of *N*-substituted benzisoxazolinones **252**.

Unlike *N*-alkyl and *N*-aryl benzisoxazoline-3-ones syntheses, only one example of the preparation of *N*-alkoxy derivatives has been reported.[194] It was shown that one-pot PIFA oxidation of *O*-alkylated hydroxamic acid derivative **254** afforded the desired *N*-alkoxy-benzisoxazoline-3-one **255** in poor yield. However, a sequential treatment of starting hydroxamic acid **254** with *tert*-butyl hypochlorite and silica gel gave the target lactam **255** thorough the formation of *N*-chloro derivative **256** in quantitative yield (Scheme 57).



Scheme 57. Synthesis of *N*-alkoxybenzisoxazolinones **255**.

As shown above, in most cases the C–O or N–O bond formation in starting hydroxamic acids was accomplished. However, benzisoxazoline-3-ones can be obtained from 4,5-diarylisoxazole-3-ones by benzene ring formation. For instance, oxidative cyclization of *N*-alkylated diaryl isoxazolone **257** derivative under irradiation with UV-light (265 nm) in ethanol afforded polycyclic benzisoxazolin-3-one derivative **258** (Scheme 58).[195]



Scheme 58. Photocyclization of diarylisoxazolone **257**.

6. Conclusions

The benzisoxazole scaffold finds broad applications in various areas making the synthesis of this heterocyclic moiety highly important. Classic approaches, such as base-induced ring closure, are still used, but have some limitations. Development of organic chemistry led to the formation of new modular synthetic methods: [3+2]-cycloaddition reactions of arynes or quinones and metal-catalyzed [4+1]-annulations that give both benzisoxazoles and benzisoxazolines. Synthesis of benzisoxazoles from substituted isoxazole derivatives by benzene ring formation is of particular importance. Unlike C–O and N–O bond formation approaches, it allows more efficient installation of substituents in the benzene part of benzisoxazole core.

The emergence of these new methods has overcome some of the limitations of classical approaches. However, there are some issues to be solved. Unlike benzisoxazoles, benzisoxazolines have the chiral center at C-3, and therefore synthesis of the specific optical isomer is an important task. In particular, an asymmetric synthesis of 1,2-benzisoxazolines is scarcely known. The only example was performed *via* the chiral pool synthesis from chiral pentose-based nitrones, but there are no reports about asymmetric catalysis. Preparation of benzisoxazoles bearing functionalities at C-3 (*e.g.* vinyl, alkynyl, CO_2Alk, OAryl, *etc.*) is another difficulty. Classical approaches and new aryne based methodologies still have some limitations for the synthesis of these derivatives. Finally, synthesis of 3-alkoxy-benzisoxazoles and *N*-substituted benzisoxazoline-3-ones, which are used for further transformation into biologically active derivatives, is still performed in most cases by direct alkylation of starting benzisoxazolinones. This step is not selective, and efficient preparation of these compounds, especially *N*-substituted derivatives, is an unsolved task. We hope

this review will give insight into the synthesis of 1,2-benzisoxazoles and related compounds and will encourage scientists to develop new or modify existing synthetic approaches to these valuable heterocycles.

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