A Platinum Open Access Journal for Organic Chemistry

Review

Free to Authors and Readers | DOAJ Seal | *Arkivoc* **2024** (5) 202312146

Synthesis of benzo[*d*]isothiazoles: an update

Yulia Ivanova,[a†] Marin Smoljo,[a†] Steven De Jonghe,[b] and Wim Dehaen[a*]

[a]*Sustainable Chemistry for Metals and Molecules, Department of Chemistry, KU Leuven, Celestijnenlaan 200F, B-3001 Leuven, Belgium*

[b]*KU Leuven, Department of Microbiology, Immunology and Transplantation, Rega Institute for Medical Research, Laboratory of Virology and Chemotherapy, Herestraat 49, box 1043, 3000 Leuven, Belgium*

[†]*These authors contributed equally to this work*

Email: wim.dehaen@kuleuven.be

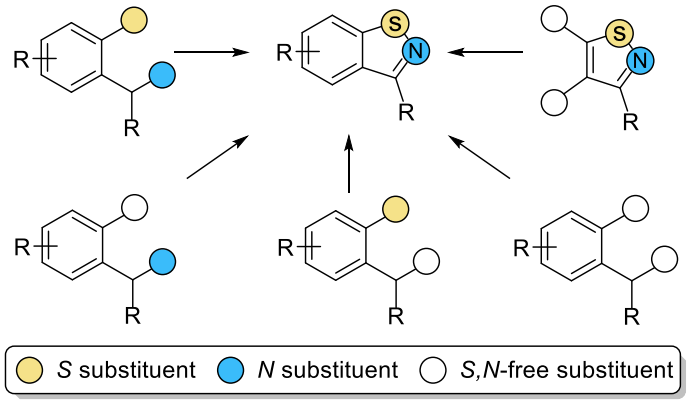
Dedicated to Prof. Dr. Léon Ghosez

Received mm-dd-yyyy **Accepted** mm-dd-yyyy **Published on line** mm-dd-yyyy

Dates to be inserted by editorial office

Abstract

An overview of the recent advancements in the synthesis of benzo[*d*]isothiazoles is provided. The synthetic approaches developed between 2010 and October 2023 are discussed and arranged in five categories according to the substrate used for the scaffold assembly. The novel synthetic methodologies contribute to the enlargement of the chemical space occupied by benzo[*d*]isothiazoles and to the exploration of its applications in various fields such as medicinal chemistry and catalysis.



Keywords: Benzo[*d*]isothiazoles, benzo[*d*]isothiazol-3(2*H*)-ones, isothiazoles, annulation

Table of Contents

1. Introduction

The isothiazole scaffold, containing two electronegative heteroatoms (sulfur and nitrogen) in a 1,2-relationship, is present in various biologically active compounds.[1–5] Its fused analogue, benzo[*d*]isothiazole, constitutes the core structure of potent inhibitors of multiple biological targets and pathways.[6–10] For instance, benzo[*d*]isothiazole *C*-glucoside **1** inhibits the activity of the sodium glucose co-transporter 2 (SGLT2) and can be used in treating type 2 diabetes.[10] Benzo[*d*]isothiazole-based compound **2** has been reported as a highly potent and selective positive allosteric modulator (PAM) for the metabotropic glutamate receptor 4 ($mGlu_4$).[8] These $mGlu_4$ PAMs show promise as a disease-modifying therapeutic option for Parkinson's disease. Better known are a series of antipsychotic drugs, such as ziprasidone,[11] lurasidone,[12] perospirone[13] and tiospirone[14] that possess in their structure a benzo[*d*]isothiazole fragment. Different subclasses of benzo[*d*]isothiazoles, one of which contains the benzo[*d*]isothiazol-3(2H)-ones featuring a hydroxyl group at the 3-position of the isothiazole moiety (tautomerizing to carbonyl), equally serve a wide array of applications.[15–17] For instance, a series of 2-phenyl benzo[*d*]isothiazol-3(2H)-ones **3** display nanomolar inhibitory activity against the 2-C-methyl-D-erythritol 4-phosphate cytidyltransferase (IspD) of *Plasmodium* spp, which is a promising target in antimalarial drug development.[15] Using benzo[*d*]isothiazol-3(2*H*)-ones as a redox activator, efficient solid-phase peptide synthesis can be performed under mild conditions.[17] The oxidized analogues of benzo[*d*]isothiazoles are of interest due to their biological activity such as HIV-1 inhibitors or plant defense activators (e.g. probenazole) (Figure 1).[18–23]

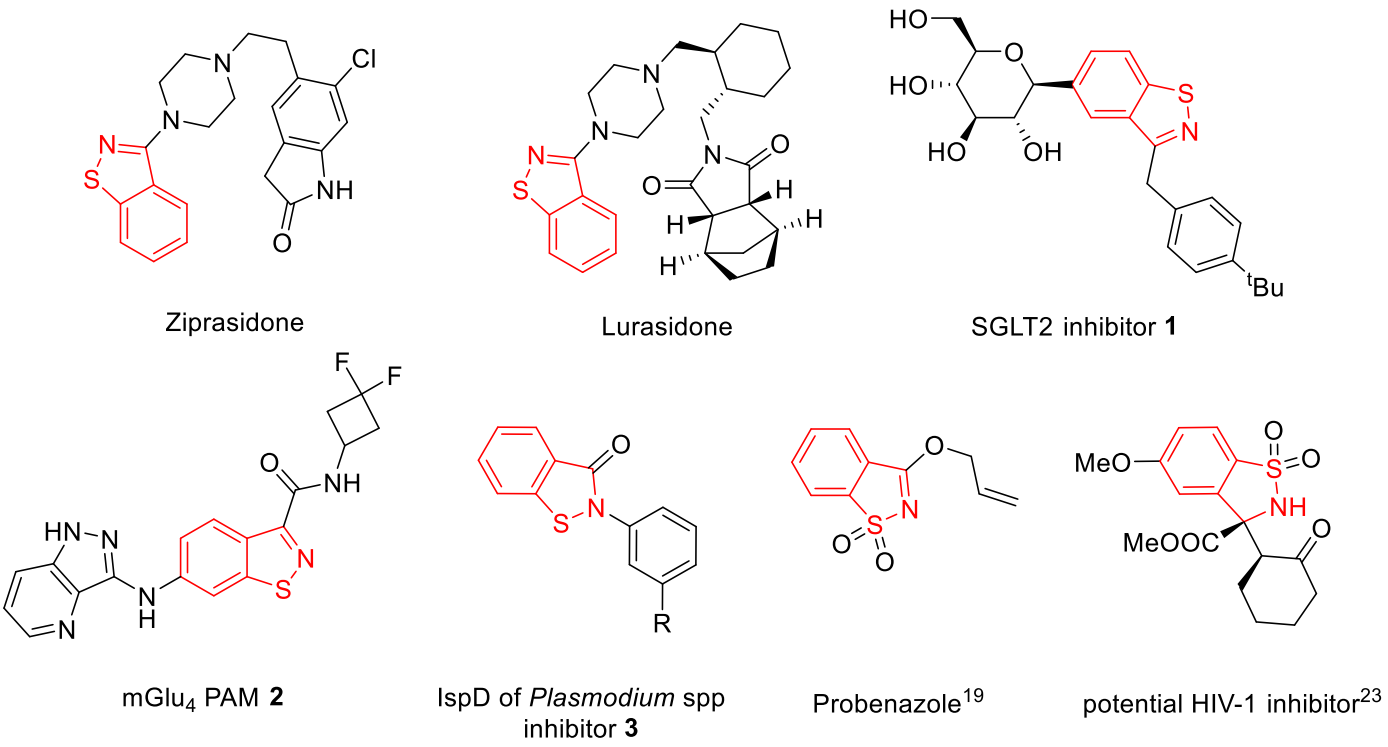


Figure 1. Biologically-active benzo[*d*]isothiazole derivatives (benzisothiazole scaffold highlighted in red).

After being prepared for the first time in 1956, the physical and chemical properties of the parent isothiazole have been extensively studied.[24] However, benzisothiazoles have an even longer history than isothiazoles. Specifically, a derivative of the most widely known benzo[*d*]isothiazole, saccharin **4**, was first obtained in 1879 (Figure 2).[25] Despite this early discovery of benzo[*d*]isothiazoles **5**, a limited number of synthetic pathways towards this scaffold and its constitutional isomer, benzo[*c*]isothiazole **6**, was available until recently. This is particularly interesting as there are numerous synthetic methods of its other constitutional isomer, benzothiazole **7**, and its derivatives.[26,27]

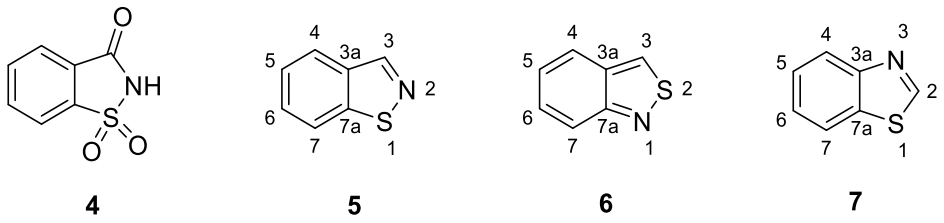
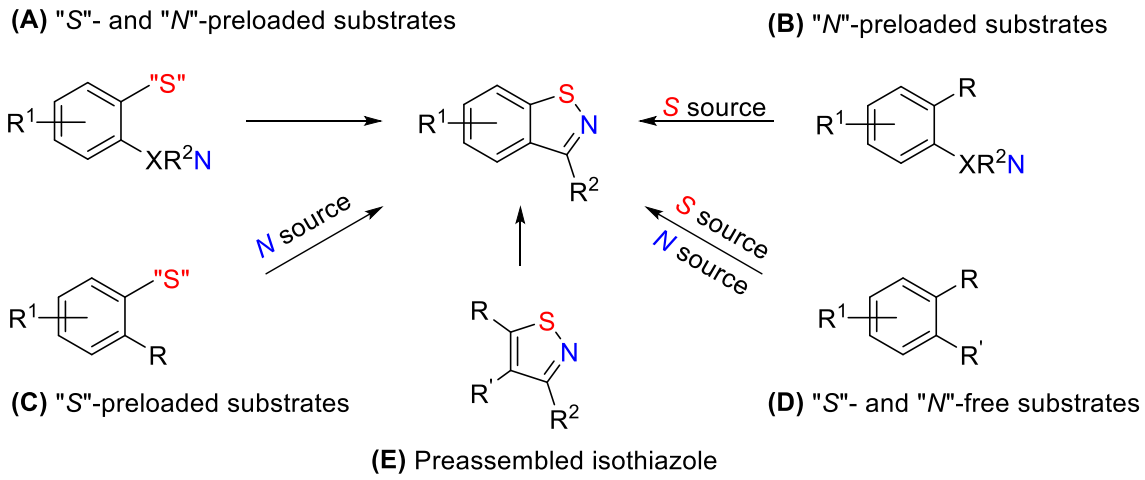


Figure 2. Structures of saccharin **4**, benzo[*d*]isothiazole **5,** benzo[*c*]isothiazole **6**, and benzothiazole **7**.

Some previously existing methods for the preparation of benzo[*d*]isothiazole derivatives required cumbersome synthetic procedures and harsh reaction conditions.[28,29] The last decade, however, has especially witnessed major advances in the synthesis and functionalization of benzo[*d*]isothiazole derivatives. There is a scarcity of comprehensive reviews covering the synthetic pathways to prepare benzo[*d*]isothiazoles. In 2002, an overview of existing methods was published as a book chapter that was subsequently updated by Sainsbury in 2010.[30] Two years later, another book issue was released, which included a chapter on isothiazoles and benzisothiazoles.[31] The main emphasis of this chapter, however, was on the metalation reactions involving the aforementioned heterocycles. Therefore, the aim of this review is to give an overview of the recent

developments in the synthesis of benzo[*d*]isothiazoles. To provide complementarity to the existing reviews, mainly novel methods described from 2010 onwards will be discussed.

The majority of the procedures for the construction of the benzo[*d*]isothiazole scaffold involves an assembly of the heterocyclic part. These approaches utilise substituted phenyl substrates, and can be divided into four categories based on the presence or absence of heteroatoms (sulfur and nitrogen) in the starting material (Scheme 1). The most commonly used strategy for preparing benzo[*d*]isothiazoles employs nitrogen and sulfur pre-functionalized phenyl rings as building blocks (Scheme 1A). Using only a nitrogen-preloaded substrate is an alternative pathway for the isothiazole ring synthesis (Scheme 1B). The third approach is to engage sulfur-preloaded phenyl substrates (Scheme 1C). Lastly, the fourth method for the preparation of benzo[*d*]isothiazoles starts from substrates that contain neither nitrogen nor sulfur (Scheme 1D). While these four categories describe the formation of the isothiazole moiety onto a substituted phenyl ring, an alternative, much less explored pathway involves assembling the aryl ring onto an existing isothiazole (Scheme 1E). Hence, five synthetic routes for the preparation of benzo[*d*]isothiazoles will be discussed in this review. If applicable, each category will be divided into two subsections, describing the preparation of benzo[*d*]isothiazol-3(2*H*)-ones (further referred to as benzo[*d*]isothiazolones unless mentioned otherwise) and other benzo[*d*]isothiazoles, respectively. This division is chosen because of the great differences in starting materials to synthesize both subseries. The *S*-oxidized analogues of benzo[*d*]isothiazoles are commonly obtained *via* oxidation of already available scaffolds[32] and, therefore, will not be discussed in detail.



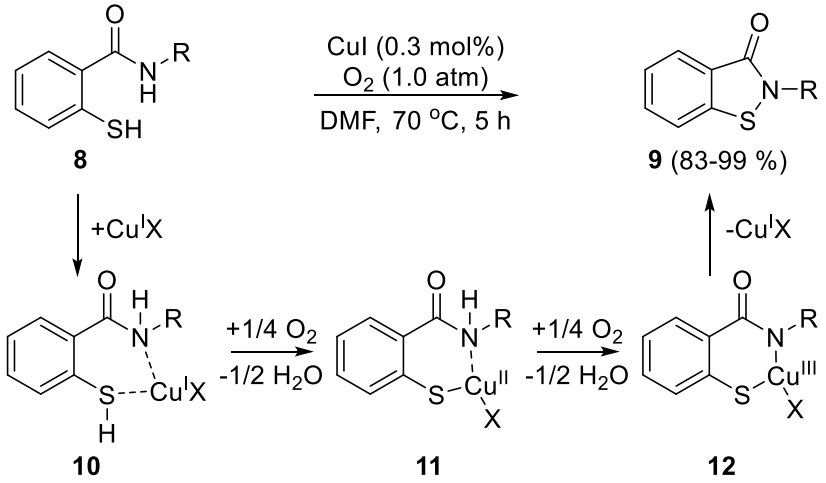
Scheme 1. General classification of synthetic methods for the preparation of benzo[*d*]isothiazoles from aromatic substrates. ”R”, “R’”, “R^1” and “R^2” are general substituents of various nature which will be discussed in further chapters. “X” stands for sp^2- or sp^3-hybridized carbon atoms.

2. Synthesis of Benzo[*d*]isothiazoles from Nitrogen and Sulfur Preloaded Aromatics

2.1. Benzo[*d*]isothiazol-3(2*H*)-ones

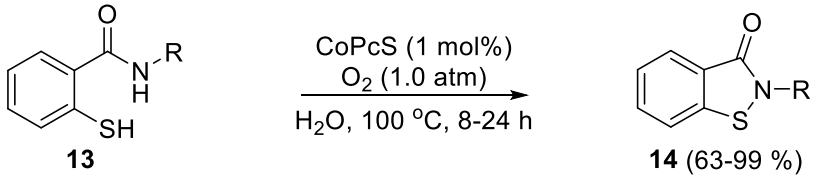
Intramolecular oxidative N-S bond formation is a well-known approach towards non-fused isothiazoles[33,34], which can be expanded to the fused analogues when starting from appropriately substituted phenyl precursors. Implementing this strategy, 2-mercaptobenzamides became commonly used substrates for the transition-metal-assisted synthesis of benzo[*d*]isothiazolones. In 2013, Kanai *et al.* developed a gram-scale synthesis by treating various 2-mercapto-*N*-substituted benzamides **8** with a catalytic amount of copper(I) iodide in DMF at

70 °C under oxygen atmosphere to obtain 2-substituted benzo[*d*]isothiazolones **9** (Scheme 2).[35] The scope included *N*-aryl and *N*-alkyl lactams, showing a high functional-group tolerance. The reaction was also applied to the synthesis of a precursor of piroxicam, a marketed anti-inflammatory drug. The proposed mechanism includes the sequential ligation to, and oxidative insertion of, copper(I) into the bidentate starting material. The copper facilitates the N-S bond formation by reductive elimination of a six-membered *N,S*-containing cupracycle **12**. Conducting the reaction in an oxygen-free environment did not lead to the desired product, supporting the proposed mechanism.



Scheme 2. Formation of benzo[*d*]isothiazolones from 2-mercapto-*N*-substituted benzamides, catalyzed by copper(I) iodide. [35]

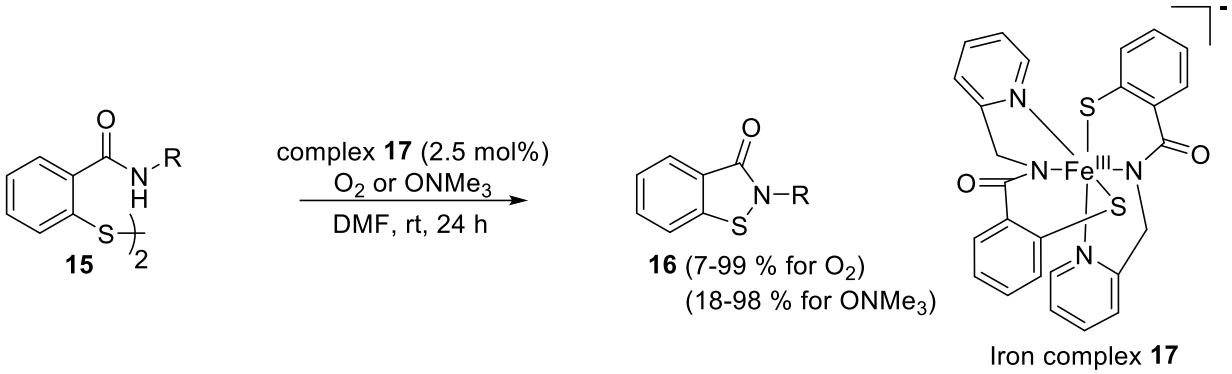
Using highly similar substrates **13**, the Yang group applied cobalt to catalyse the oxidative N-S bond formation (Scheme 3).[36] In a previous study,[37] the authors developed a general N,S-bond formation strategy in water under oxygen atmosphere with CoPcS (cobalt phthalocyanine-tetrasodium sulfonate) as the optimal catalyst, which could efficiently induce ring-closure towards benzoisothiazolones **14**. The substrate scope was exemplified with diverse aryl and alkyl substituents on the nitrogen. Apart from the broad scope, the aqueous medium facilitated purification as the products often precipitated from the reaction mixture. The medium and catalyst were recycled six times, proving the sustainability of this method.



Scheme 3. Formation of benzo[*d*]isothiazolones from 2-mercapto-*N*-substituted benzamides, catalyzed by cobalt phthalocyanine-tetrasodium sulfonate.[36]

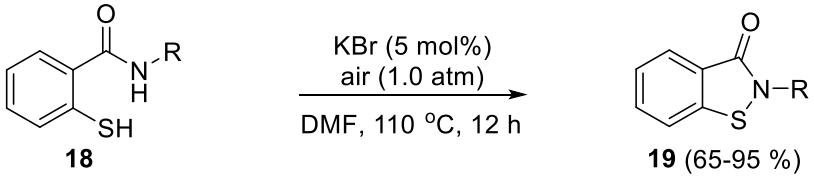
In 2018, Horng and coworkers showed that molecular oxygen can be activated by iron complexes.[38] Four years later, the same group employed this process for the synthesis of benzo[*d*]isothiazolones **16** from the 2,2'-disulfanediyldibenzamides **15** (Scheme 4).[39] Oxygen or trimethylamine *N*-oxide (a milder O-donor) were used as oxidants, with overall higher yields for the latter. In contrast to the previous metal-catalysed methods, the iron complex does not require elevated reaction temperatures. Interestingly, both the dinuclear iron (II) complex

and mononuclear iron (III) complex **17** successfully facilitate N-S bond formation; the latter was chosen as the main catalyst due to its greater stability.



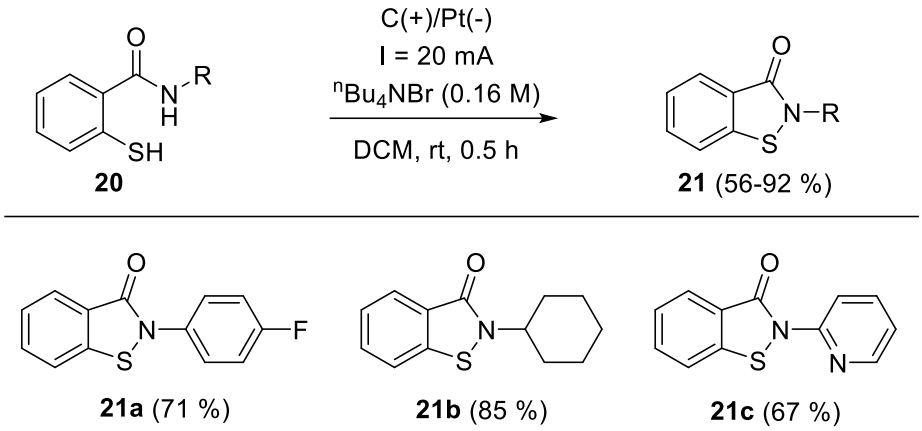
Scheme 4. Formation of benzo[*d*]isothiazolones from 2,2'-disulfanediyldibenzamides, catalyzed by mononuclear iron (III) complex **17**. [39]

Besides transition-metal-catalysed methods, metal-free approaches have been developed as well. An example is an oxidative N-S bond formation starting from the *ortho*-amidoarylthiols **18** using a catalytic amount of KBr (Scheme 5).[40] Similarly to the metal-promoted cyclisations, this reaction occurs under oxygen atmosphere. Oxygen was shown to be crucial for the *in situ* oxidative formation of bromine, which oxidises the thiol by transforming it into an S-Br bond. The subsequent ring closure, by elimination of HBr, completes the catalytic bromine cycle. This reaction thus proceeds *via* a different mechanism and is a cheaper alternative to the previously discussed reactions. Several unrelated reports also describe ring-forming reactions in the presence of bromine, leading to benzo[*d*]isothiazolones.[41–43]



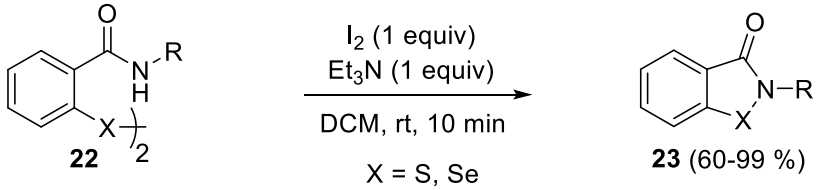
Scheme 5. Formation of benzo[*d*]isothiazolones from *ortho*-amidoarylthiols, catalyzed by potassium bromide.[40]

Another method bypassing the necessity for metal catalysts is the electrochemical synthesis developed by Chen *et al*. (Scheme 6).[44] The reaction proceeds through an intramolecular N-H/S-H coupling of the corresponding 2-mercaptobenzamides **20**, generating hydrogen gas as a side product. Under optimised conditions, high yields of various *N*-substituted benzo[*d*]isothiazolones **21** were obtained, including pyridyl as a substituent at the 2-position (**21c**).



Scheme 6. Electrochemical synthesis of benzo[*d*]isothiazolones from 2-mercaptobenzamides. [44]

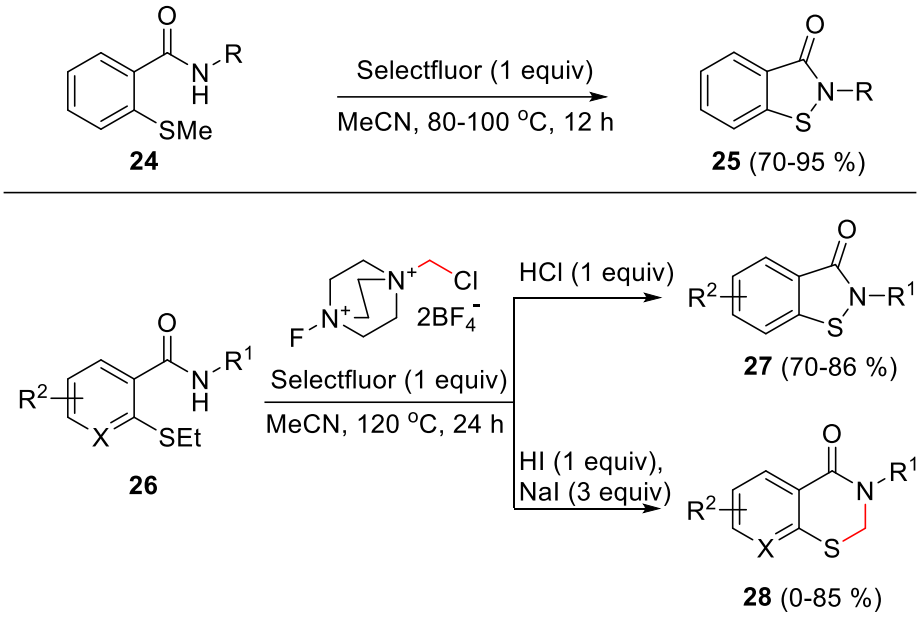
One major limitation associated with oxidative conditions is the undesirable redox reaction occurring with the organic thiols. To circumvent this, alternative starting materials, such as dimers of the related thiols, are being used. Although such substrates were already briefly discussed above (Scheme 4),[39] there are many more examples of thiol dimers as precursors for the synthesis of benzo[*d*]isothiazolones. Thus, Santi *et al*. developed a fast and easy metal-free conversion method of dimeric *ortho*-amidoaryldisulfides and *ortho*-amidoaryldiselenides **22** into fused structures **23** (Scheme 7).[45] Preliminary *in silico* studies indicated iodine to be the most promising oxidant due to formation of a stable intermediate. In accordance with the computational study, the optimised conditions revealed iodine as the best oxidant with triethylamine as an additive. While the main focus of this research was on the selenium-containing structures, the optimised procedure worked equally well for the sulfur-based analogues. The reaction scope included two *N*-aliphatic benzo[*d*]isothiazolones, obtained in quantitative yields. Another report using disulfides had a wider benzo[*d*]isothiazolones scope with yields from 38 to 75%.[46] However, this amounted to the reproduction of a known procedure of 1983,[47] which is outside the scope of this review.



Scheme 7. Formation of benzo[*d*]isothiazolones and benzo[*d*][1,2]selenazolones from *ortho*-amidoaryldisulfides and *ortho*-amidoaryldiselenides, using iodine. [45]

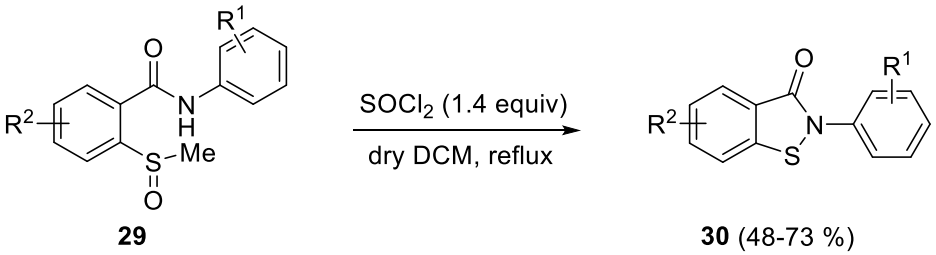
A highly efficient, oxygen- and metal-free ring-closure involves Selectfluor (Scheme 8, top).[48] Although typically used as an electrophilic fluorine donor,[49] this reagent also gained considerable interest for other types of transformations.[50] Optimization studies revealed that, instead of 2-sulfhydrylbenzamides, the corresponding methyl thioethers **24** were the preferred substrates. Additionally, an elevated reaction temperature and one equivalent of Selectfluor were required to drive the reaction to completion. Various aliphatic and aromatic 2-(methylsulfanyl)-*N*-substituted benzamides yielded a library of benzo[*d*]isothiazolones **25**. Later, another study of a metal-free transformation mediated by Selectfluor was published, starting from 2-(ethylsulfanyl)-benzamides **26** in the presence of HCl, which afforded aliphatic *N*-substituted benzo[*d*]isothiazolones **27** in yields ranging from 70 to 86% (Scheme 8, bottom). [51] In the presence of hydroiodic acid and sodium iodide, the *in situ*-

generated benzoisothiazolone ring expanded to furnish the six-membered 2,3-dihydrobenzothiazin-4-ones **28** by insertion of the chloromethylene unit of Selectfluor.



Scheme 8. **Top**: Formation of benzo[*d*]isothiazolones from 2-(methylthio)benzamides, using Selectfluor; [48] **bottom**: Formation of benzo[*d*]isothiazolones and 2,3-dihydrobenzothiazin-4-ones in the presence of hydrochloric acid or hydroiodic acid and sodium iodide, respectively. [51]

As a report from 2011 demonstrated, sulfoxide analogues of 2-mercaptobenzamides can also be efficiently converted to benzo[*d*]isothiazolones (Scheme 9).[52] Oxidation of sulfides to the corresponding sulfoxides **29** was followed by treatment with thionyl chloride, furnishing the desired fused five-membered structures **30**. The substituent scope included various groups on both phenyl groups, i.e., the phenyl that is part of the benzoisothiazole scaffold as well as the *N*-phenyl group. The same method was also employed in later research by O'Neill *et al.* affording similar structures in yields of up to 74%.[15] Benzo[*d*]isothiazolones were also formed from the sulfoxide precursors as by-products during various reactions described in the report of Zanda *et al.*[53]

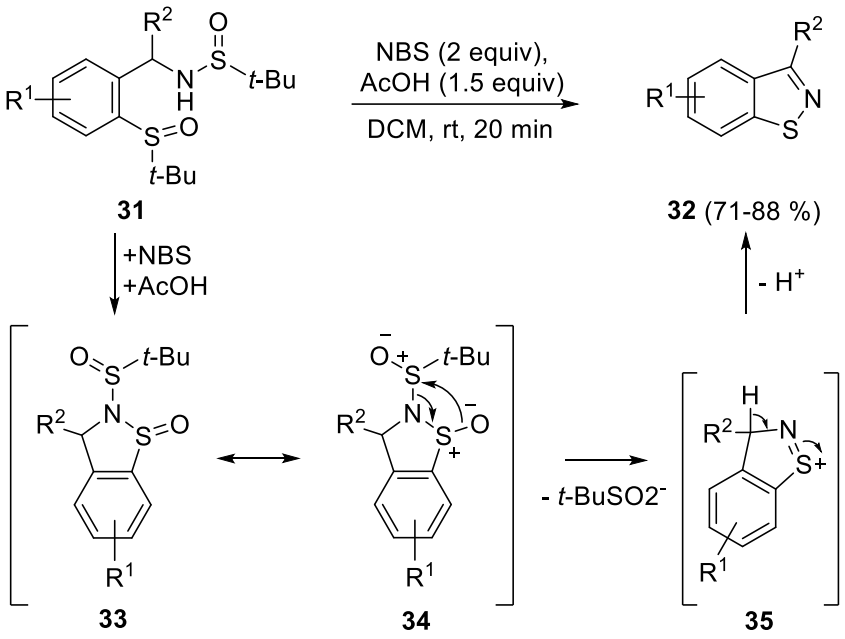


Scheme 9. Formation of benzo[*d*]isothiazolones from 2-(methylsulfinyl)benzamides, using thionyl chloride. [52]

2.2. Benzo[*d*]isothiazoles

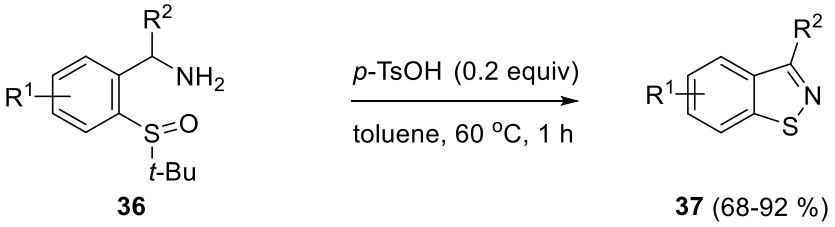
The synthesis of benzo[*d*]isothiazoles involving an all-heteroatom Wittig-equivalent process was reported by Sun *et al*. (Scheme 10).[54] This work was the continuation of a previous study, with more emphasis on benzo[*d*]isothiazole preparation.[55] The crucial steps of this reaction include the *N*-bromosuccinimide (NBS)-induced activation of the starting aryl *tert*-butyl sulfoxides **31**, followed by its conversion to sulfinimides and a Wittig-like reaction leading to benzo[*d*]isothiazole derivatives **32**. The reaction proceeds fast at room

temperature and tolerates a wide variety of substituents, particularly at the 3-position of the formed isothiazoles.



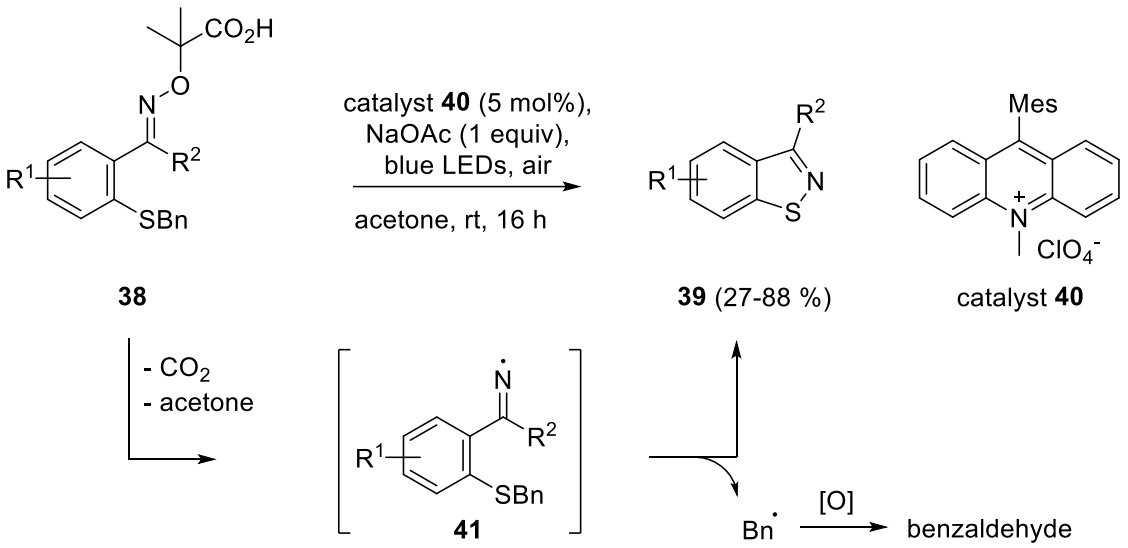
Scheme 10. Formation of benzo[*d*]isothiazoles from aryl *tert*-butyl sulfoxides, using *N*-bromosuccinimide.[54]

More recent work by the same group describes an improved method to efficiently prepare benzo[*d*]isothiazole derivatives (Scheme 11).[56] This novel procedure avoids NBS and, instead, employs amine **36** as the nucleophile in the presence of a catalytic amount of *p*-toluenesulfonic acid (*p*-TsOH) in toluene. Interestingly, the reaction also proceeds well without any acid additive, albeit at higher temperatures and with a longer reaction time.



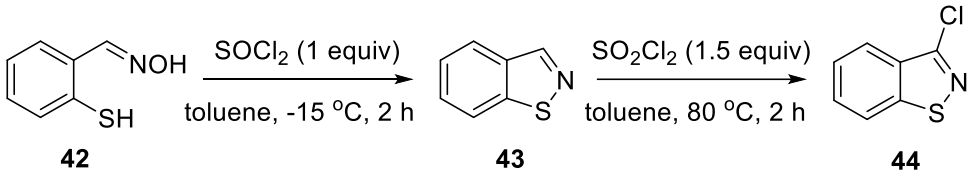
Scheme 11. Formation of benzo[*d*]isothiazoles from aryl *tert*-butyl sulfoxides, using *p*-toluenesulfonic acid.[56]

The metal-free, visible-light-promoted synthesis of benzo[*d*]isothiazoles **39** is of particular interest from a sustainability point. (Scheme 12)[57] The N-S bond of isothiazoles is formed under mild conditions from α-amino-oxy acids **38** through the generation of iminyl radicals **41**, facilitated by blue-light irradiation and the commerciallyavailable acridinium photocatalyst **40**. The green aspect of the procedure is highlighted not only by the formation of benign secondary products (carbon dioxide, benzaldehyde and acetone), but also by the implementation of a continuous flow-setup. Interestingly, this strategy is less suitable for the synthesis of benzo[*d*]isothiazoles that are unsubstituted at the 3-position, as indicated by their significantly lower yield (27%) compared to 3-substituted derivatives.



Scheme 12. Formation of benzo[*d*]isothiazoles from α-amino-oxy acids, using acridinium photocatalyst. [57]

The synthesis of the non-functionalised benzo[*d*]isothiazole **43** received little attention due to its limited applications. The fused ring can be obtained from benzaldehydeoxime-2-thiol **42** by ring closure with thionyl chloride in toluene (Scheme 13). The 3-position can be chlorinated by sulfuryl chloride, however, allowing further functionalisation. [58]

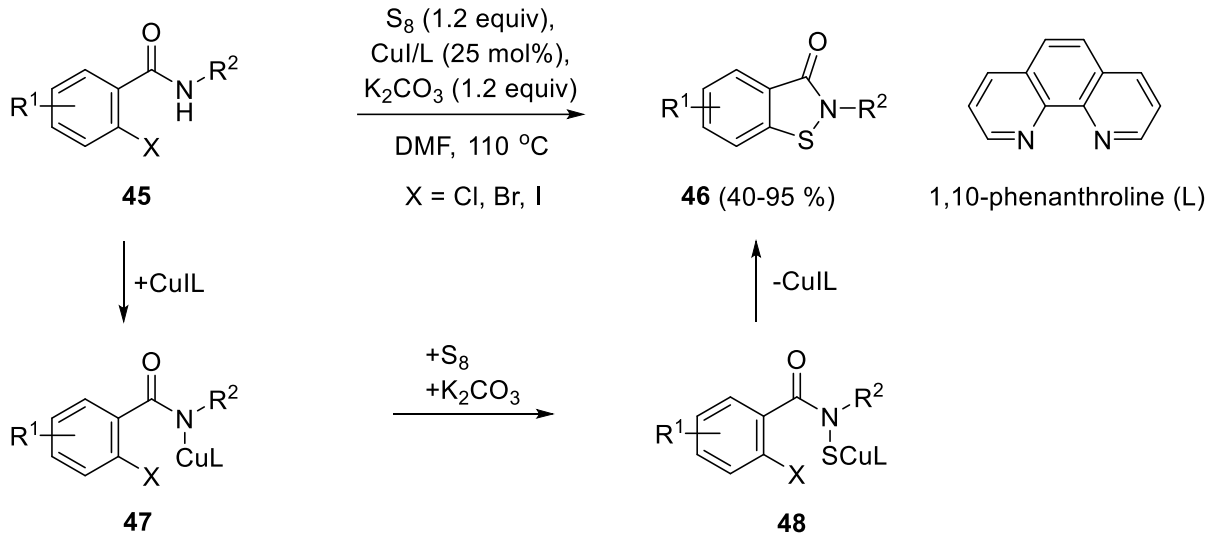


Scheme 13. Formation of benzo[*d*]isothiazoles from benzaldehydeoxime-2-thiol, using thionyl chloride. [58]

3. Synthesis of Benzo[*d*]isothiazoles from Nitrogen Preloaded Aromatics

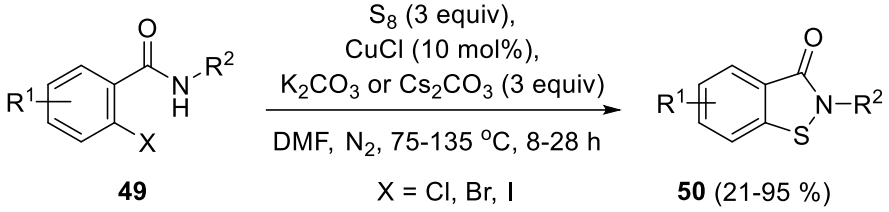
3.1. Benzo[*d*]isothiazol-3(2*H*)-ones

Sulfur powder is the most evident reagent as the source for assembling sulfur containing heterocycles. Thus, benzo[*d*]isothiazolones **46** can be prepared from commercially available 2-halo-benzamides **45** *via* a copper-mediated reaction with elemental sulfur.[59] The same reaction conditions were used before to prepare selenium-containing compounds[60] and have been implemented recently to obtain a library of *N*-substituted benzo[*d*]isothiazolones in yields of up to 95%. According to the authors, the proposed mechanism proceeds *via* a ligand-copper-amide nitrogen complex **47** formation, followed by sulfur insertion under basic conditions. Intramolecular reaction with the carbon-halogen bond, followed by reductive elimination furnishes the benzo[*d*]isothiazolone ring. Since there is no clear evidence for the existence of intermediate **48**, a similar mechanism to the one shown in Scheme 2 might as well be plausible. Almost identical reaction conditions were used by Krasikova and Katkevics for the preparation of benzo[*d*]isothiazolones in yields from 15 to 94%.[61]



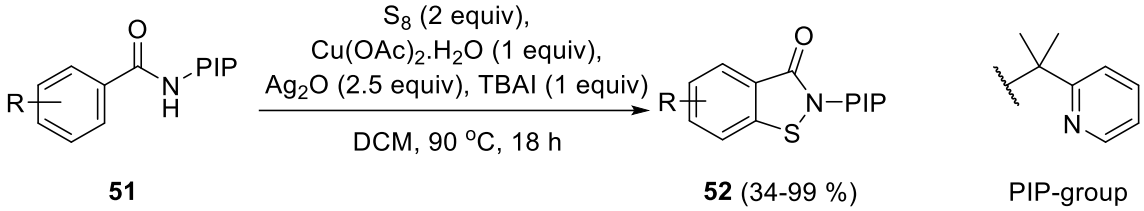
Scheme 14. Formation of benzo[*d*]isothiazolones from 2-halo-benzamides, catalyzed by copper(I) iodide. [59]

The same year, additional research involving molecular sulfur was published (Scheme 15).[62] This time, copper chloride was used in the absence of a ligand, and the reaction was conducted under a nitrogen atmosphere. Different aryl halides **49** were evaluated as starting materials, with the aryl iodides leading to higher reaction yields and shorter reaction times. For instance, the reaction with *N*-benzyl-2-iodo-5-nitrobenzamide yielded the desired product in 85% yield after 8 hours, while the corresponding chloro derivative afforded the target compound in only 35% yield in 28 hours. The scope included various alkyl and aryl derivatives **50** obtained in high yields, and the final structure was verified by X-ray analysis for one particular compound.



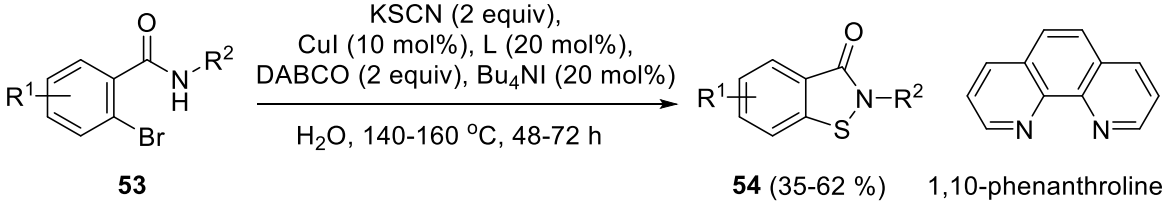
Scheme 15. Formation of benzo[*d*]isothiazolones from 2-halo-benzamides, catalyzed by copper(I) chloride. [62]

In 2014, Wu, Shi and co-workers reported a method for the synthesis of benzo[*d*]isothiazolones **52**, relying on a copper(II)-mediated C-S/N-S bond formation (Scheme 16).[63] Benzamides **51,** derived from (pyridin-2-yl)isopropylamine (PIP-amine) and benzoic acids, were coupled with molecular sulfur under aerobic conditions in DCM at 90 °C. The optimised system employs $Cu(OAc)_2.H_2O$ as a promoter for C-H activation in the presence of the oxidant Ag_2O and the additive tetrabutylammonium iodide (TBAI). This procedure allows the synthesis of various aryl-substituted benzo[*d*]isothiazolones in moderate to high yields, with electron-withdrawing groups on the phenyl moiety generally leading to higher reaction yields. The method is also compatible with heterocyclic substrates, thus allowing access to a broad range of unique heteroaryl-[*d*]-fused isothiazolones. The obtained benzo[*d*]isothiazolones were transformed into versatile sulfur-containing compounds *via* a ring-opening reaction, although the cleavage of the PIP group was not discussed.



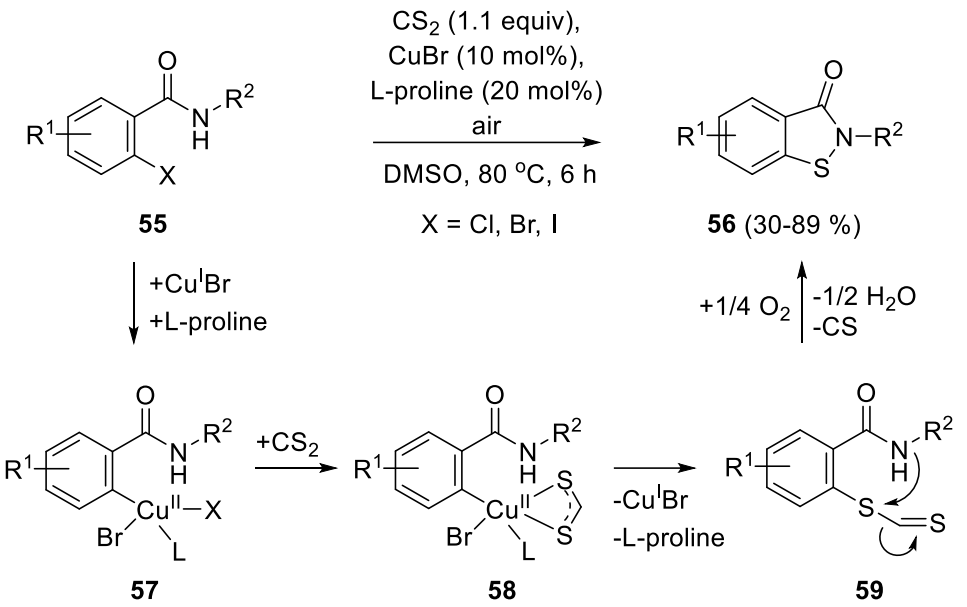
Scheme 16. Formation of benzo[*d*]isothiazolones from *N*(2-(pyridin-2-yl)propan-2-yl)benzamides, using copper(II) acetate. [63]

While sulfur powder is the most abundantly used reagent as the source of this element, alternative reagents exist for the same purpose. For instance, a copper-catalysed tandem reaction of 2-bromobenzamide **53** with potassium thiocyanate (KSCN) affording benzo[*d*]isothiazolones **54** has been reported.[64] The optimization study revealed that water was the optimal solvent, and that organic bases (such as Et_3N and 1,4-diazabicyclo[2.2.2]octane (DABCO)) were preferred over the inorganic ones. The scope of this procedure included several *N*-unsubstituted and *N*-alkyl-isothiazolones fused with various aryl groups. Interestingly, for the latter, elevated temperature (160 °C, instead of the usual 140 °C) was needed to drive the reaction to completion. The procedure was not applicable to the synthesis of aryl *N*-substituted benzo[*d*]isothiazolones, most likely due to the weaker nitrogen nucleophilicity of the starting amides.



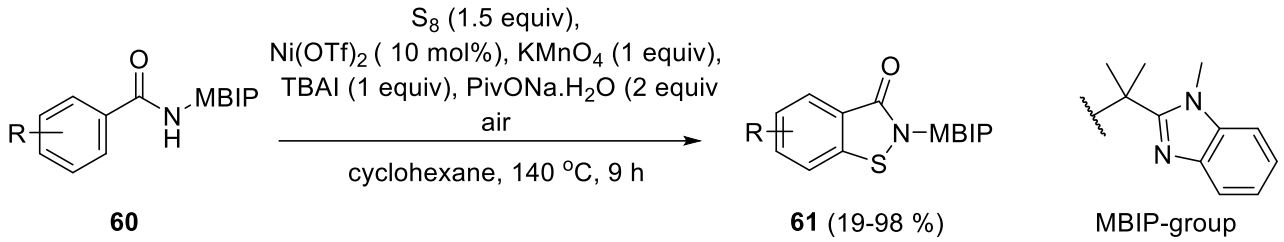
Scheme 17. Formation of benzo[*d*]isothiazolones from 2-bromobenzamides, using potassium thiocyanate. [64]

Carbon disulfide (CS_2) has been used as an alternative sulfur source for benzo[*d*]isothiazolones **56** preparation (Scheme 18).[65] Similarly to the previously described reactions, a copper catalyst (copper bromide) was needed to facilitate the product formation in a desirable yield. Copper oxidative addition to the 2-halobenzamides **55**, assisted by L-proline, begins the catalytic cycle of the reaction mechanism, explaining the higher yields obtained with the 2-iodobenzamides when compared to the 2-chlorobenzamides. In the next step, a ligand exchange happens, forming an intermediate **58** with CS_2. The following insertion of CS_2 into the Cu-C bond, along with reductive elimination furnishes the intermediate **59**, which undergoes an intramolecular nucleophilic substitution to produce the benzo[*d*]isothiazolones **56**. The reaction conditions generally showed a high functional group tolerance, with electron-neutral and electron-donating substituents on *N*-aryl groups, giving higher yields.



Scheme 18. Formation of benzo[*d*]isothiazolones from 2-halobenzamides, using carbon disulfide. [65]

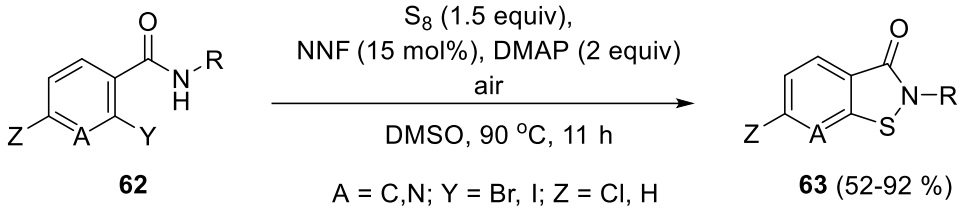
Copper is not the only transition metal catalyst for cross-coupling reactions leading to benzo[*d*]isothiazolones. The first nickel-catalysed generation of benzo[*d*]isothiazolones **61** *via* direct C–H activation was reported by Song *et al*. (Scheme 19).[66] The method was inspired by the aforementioned PIP-amine-assisted synthesis[63] and by their previous research on the application of 2-amino alkylbenzimidazole (MBIP-amine) as the directing group.[67] Yields up to 98% were obtained with a broad substrate variation, using sulfur powder as the source of sulfur, nickel(II) trifluoromethanesulfonate as the catalyst, and potassium permanganate as the oxidant. Tetra-*n*-butylammonium iodide and sodium pivalate were used as additives, both playing a crucial role during the C-H activation process. Since the activation of the directing group is an important aspect of this chemistry, an additional group-optimization study was conducted. *N*,*N*-Bidentate groups, such as PIP-amine and 8-aminoquinoline, led to the formation of the desired product, albeit in lower yields. Other aromatic and heteroaromatic groups did not succeed in promoting the reaction, indicating the specific fit of MBIP-amine for this particular transformation.



Scheme 19. Formation of benzo[*d*]isothiazolones from *N*-(2-(1-methyl-1H-benzo[*d*]imidazol-2-yl)propan-2-yl)benzamide, catalyzed by nickel (II) trifluoromethanesulfonate. [66]

An efficient, ligand-free synthesis towards the fused structures, implementing a nano-nickel ferrite (NNF) catalyst and inexpensive sulfur powder as a chalcogenation agent, has been developed (Scheme 20).[68] The optimised reaction conditions used two equivalents of base (4-dimethylaminopyridine) and 15 mol% of nickel catalyst, which could be reused for up to five runs. The scope of this procedure included various aryl, heteroaryl and alkyl substituents on the nitrogen of the isothiazole ring. In addition, the isothiazolo[5,4-*b*]pyridin-3(2*H*)-one was successfully prepared as a rare example of a fused bisheterocyclic system, albeit with a lower yield of

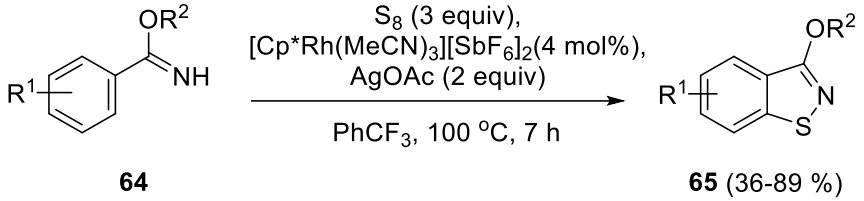
52%. A selection of the obtained benzo[*d*]isothiazolone library was further oxidised to the corresponding 1,1'-dioxide derivatives with *tert*-butyl nitrite and oxygen in high yields.



Scheme 20. Formation of benzo[*d*]isothiazolones from 2-halobenzamides, catalyzed by nano-nickel ferrite. [68]

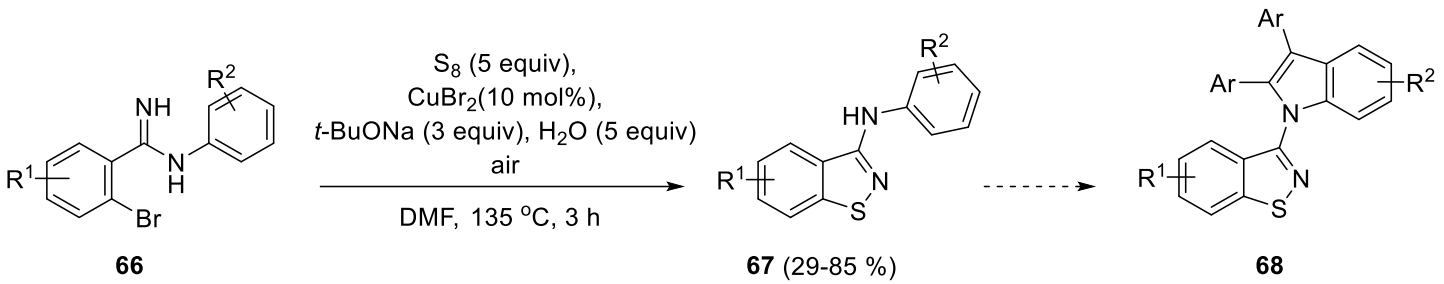
3.2. Benzo[*d*]isothiazoles

Using direct C-H activation for the construction of benzo[*d*]isothiazoles is an efficient method as it allows the implementation of imidate derivatives as readily available nitrogen sources (Scheme 21). Thus, Miura and co-workers developed a rhodium-catalysed oxidative annulation of benzimidates **64** for the assembly of various benzo[*d*]isothiazoles **65**.[69] The optimised conditions utilize elemental sulfur, $[Cp^*Rh(MeCN)_3][SbF_6]_2$ as the catalyst (Cp^* = pentamethylcyclopentadienyl) and AgOAc as the oxidant in $PhCF_3$ as the solvent at 100 °C. The mechanism of the transformation, involving a Rh(I)/Rh(III) redox reaction, was supported by DFT calculations and by the step-by-step procedure of the rhodacycle preparation and further stoichiometric reaction with elemental sulfur. The optimised procedure works equally well for the preparation of the selenium-containing analogue.



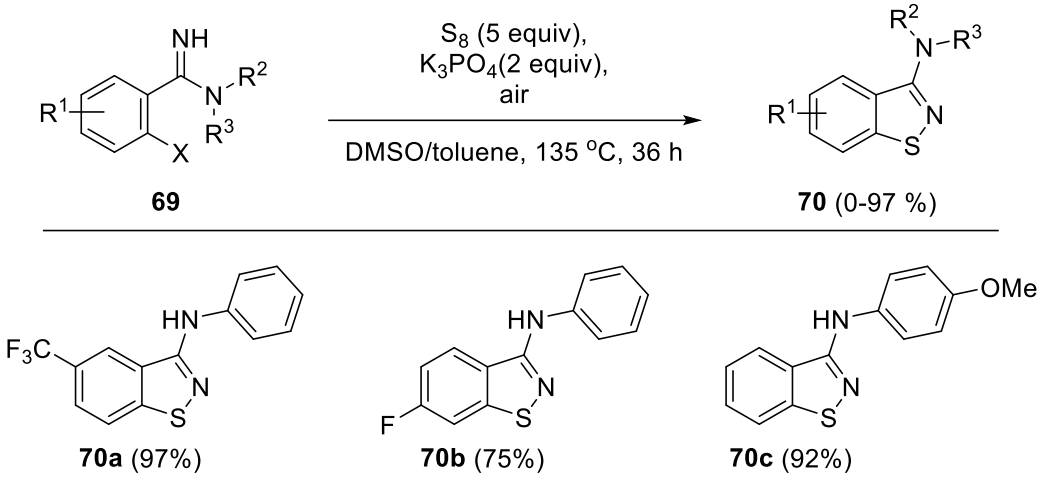
Scheme 21. Formation of benzo[*d*]isothiazoles from benzimidates, catalyzed by rhodium catalyst. [69]

As described above, copper (I) catalysts were abundantly used for the assembly of benzo[*d*]isothiazolones. Recently, a procedure using a copper (II) salt for the synthesis of benzo[*d*]isothiazoles **67** from 2-bromo-*N*-arylbenzimidamides **66** was reported (Scheme 22).[70] The annulation proceeds under alkaline and aerobic conditions using sulfur powder in DMF as a solvent. Notably, other copper (I) and copper (II) salts such as CuI, CuCl and $CuSO_4$ also exhibit good catalytic activity, while the absence of any catalyst drastically decreases the yield. A substrate-scope study revealed a high tolerance towards diverse functional groups R^1 and R^2, including alkyl, alkoxy and aryl groups, as well as halogens. This method also allows for elemental selenium, leading to the benzo[*d*]isoselenazoles on a larger scale (5 mmol). A selection of the obtained benzo[*d*]isothiazoles was further converted to *N*-aryl indoles **68**, stating the new approach towards the conjugated biaryl molecules.



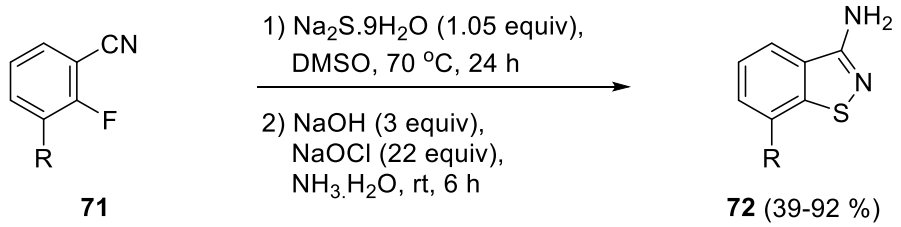
Scheme 22. Formation of benzo[*d*]isothiazoles from 2-bromo-*N*-arylbenzimidamides, catalyzed by copper (II) bromide. [70]

There is very limited research on metal-free benzo[*d*]isothiazole or benzo[*d*]isothiazolone formation from sulfur-free starting materials. A one-pot synthesis of benzo[*d*]isothiazoles **70** from *ortho*-haloarylamidines **69** and elemental sulfur through oxidative N-S/C-S bond formation has been reported by Deng et al. (Scheme 23).[71] However, the desired reactivity was achieved only at a relatively high temperature of 135 °C and after a long reaction time. The oxidative cyclization proceeds smoothly with electron-donating groups on the *N*-phenyl ring of the amidine moiety and electron-withdrawing moieties on the other phenyl ring.



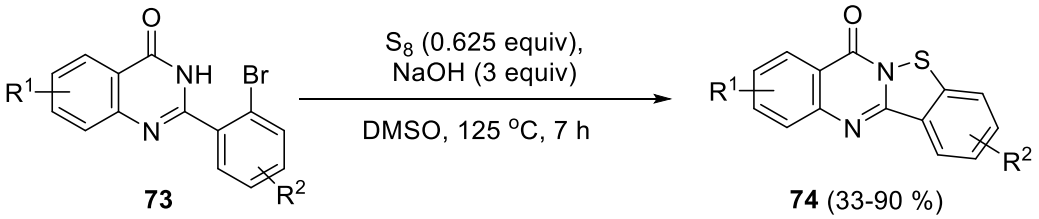
Scheme 23. Formation of benzo[*d*]isothiazoles from *ortho*-haloarylamidines, using potassium phosphate. [71]

An efficient metal-free method for benzo[*d*]isothiazole preparation was described by Wang *et al*. (Scheme 24).[9] While the main focus of the research was the development of new, medicine-related, compounds, a small scope of benzo[*d*]isothiazol-3-amines **72** was obtained. In the first step, sodium sulfide is reacted with the 3-substituted-2-fluoro-benzonitrile **71** in a nucleophilic aromatic substitution. Then, the obtained intermediate is directly reacted with ammonia and sodium hypochlorite to furnish the benzo[*d*]isothiazol-3-amine core.



Scheme 24. Formation of benzo[*d*]isothiazoles from 3-substituted-2-fluoro-benzonitrile, using sodium sulfide and sodium hypochlorite. [9]

More elaborate scaffolds, including a benzo[*d*]isothiazole fragment in their core structure, can be obtained in a comparable manner (Scheme 25). Thus, the formation of benzo[4,5]isothiazolo[3,2-*b*]quinazolinones **74** through N-S/C-S bond coupling was reported.[72] The benzo[*d*]isothiazole part is constructed with molecular sulfur under basic medium at elevated temperature. Due to the nitrogen in the starting substrate being conjugated to the carbonyl bond, no additional oxidant was needed to assemble the desired scaffold.

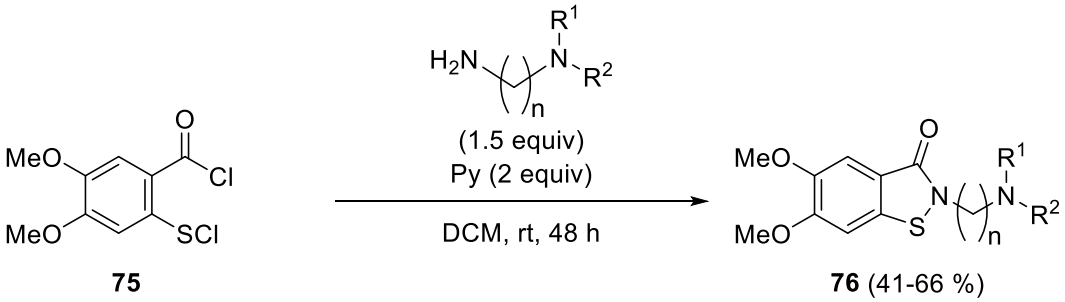


Scheme 25. Formation of benzo[4,5]isothiazolo[3,2-*b*]quinazolinones through N-S/C-S bond coupling.[72]

4. Synthesis of Benzo[*d*]isothiazoles from Sulfur Preloaded Aromatics

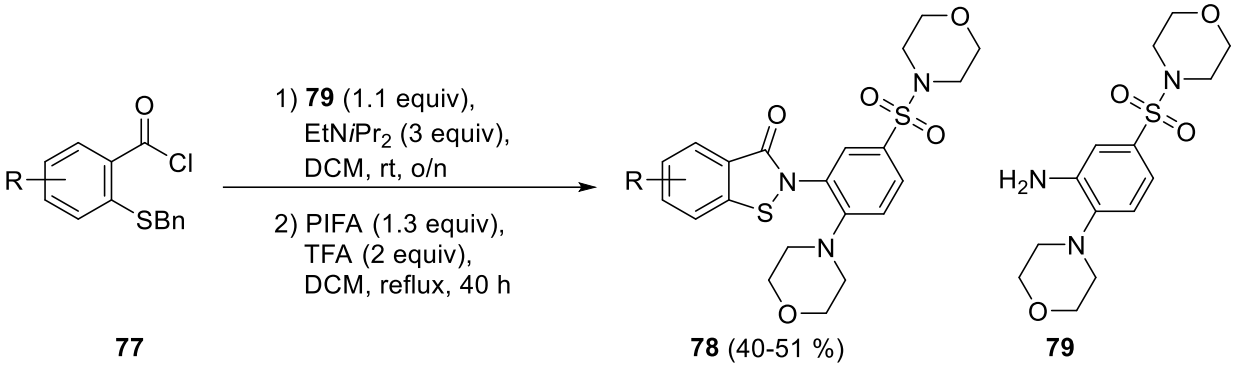
4.1. Benzo[*d*]isothiazol-3(2*H*)-ones

Benzo[*d*]isothiazolones **76** can be easily assembled in basic medium from the highly reactive 2-(chlorocarbonyl)phenyl hypochlorothioites **75** and primary amines (Scheme 26).[73] The initial procedure was described in 1986[74] and was implemented in more recent work to obtain a library of *N*-substituted benzo[*d*]isothiazolones **76** with yields from 41 to 66%. The *N*-unsubstituted scaffold was successfully constructed using ammonia solution in water. More recent work of Piomelli *et al*. used a similar approach to construct monoacylglycerol lipase (MGL) inhibitors, which included a benzo[*d*]isothiazolone fragment in their structure.[75]



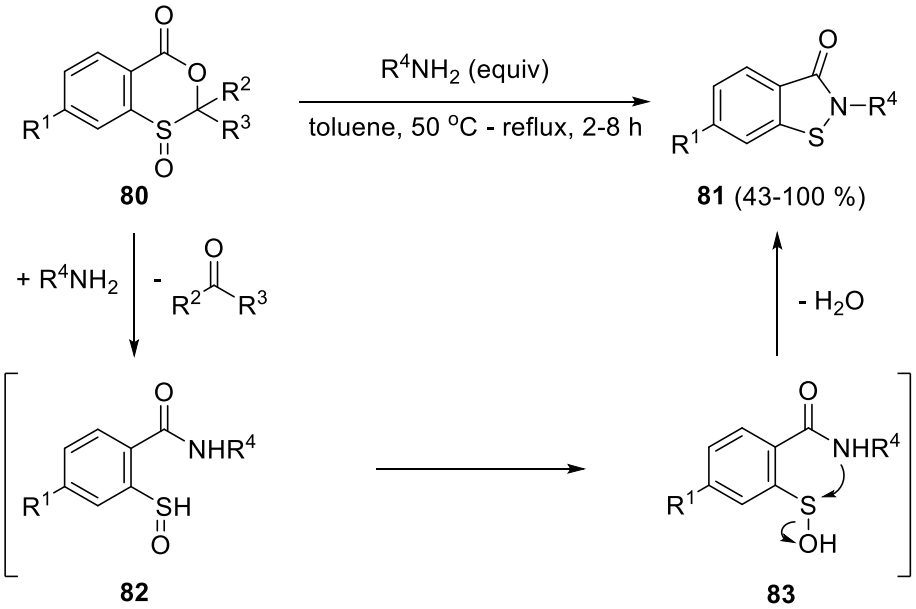
Scheme 26. Formation of benzo[*d*]isothiazolones from -(chlorocarbonyl)phenyl hypochlorothioites.[73]

The first study describing the formation of benzo[*d*]isothiazolone utilising (bis(trifluoroacetoxy)iodo)-benzene (PIFA) was reported in 2006.[76] Since then, this approach has been implemented in several recent syntheses in various fields. Frequently, the intermediate amides are freshly obtained and used directly in the cyclisation reaction, as, for example, in the work of Leissring and coworkers (Scheme 27).[77] Generally, the mechanism of the reactions using PIFA is based on the generation of an *N*-acylnitrenium ion, followed by an intramolecular reaction with sulfur to yield the *N*-aryl benzo[*d*]isothiazolones. Cosford *et al*. published a series of articles relying on the same approach towards the synthesis of fused isothiazolones.[78–80] Both *N*-aryl and -alkyl substitution on the isothiazolone ring was attained in this way.



Scheme 27. Formation of benzo[*d*]isothiazolones using (bis(trifluoroacetoxy)iodo)-benzene. [77]

Alternatively, the benzo[*d*]isothiazolone scaffold **81** can also be obtained *via* a ring-transformation reaction, as described in a 2012 report (Scheme 28).[81] The starting 1,3-benzoxathiin-4-one 1-oxides **80** are accessible *via* an improved oxidation procedure from 1,3-benzoxathiin-4-ones. The transformation reaction conditions were then optimized revealing that aprotic solvents, such as toluene or THF, were preferred over protic ones. Aliphatic and aromatic amines reacted with the cyclic precursor **80** to obtain the desired products in up to quantitative yields. Reactions with anilines and sterically hindered amines, like *tert*-butylamine, were less efficient and required higher temperatures. The proposed mechanism proceeds through the attack of an amine on the carbonyl group, resulting in the formation of amide and sulfenic acid functionalities (**82**). The nitrogen of the amide further attacks the sulfur atom and subsequent water elimination results in the formation of isothiazolone.

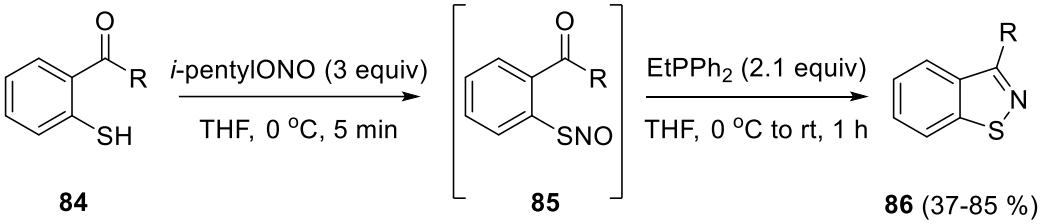


Scheme 28. Formation of benzo[*d*]isothiazolones from 1,3-benzoxathiin-4-one 1-oxides. [81]

4.1. Benzo[*d*]isothiazoles

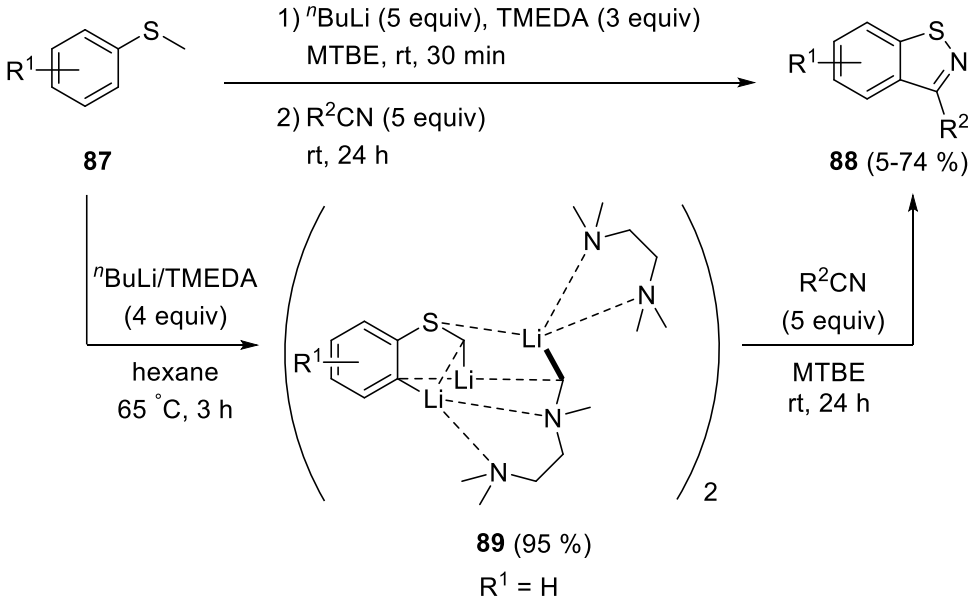
In 2010, a facile one-pot synthesis of benzo[*d*]isothiazoles **86** from readily available *ortho*-mercaptoacetophenones **84** was developed by Xian *et al*. (Scheme 29).[82] The crucial step in this process involves the formation of the *S*-nitroso intermediate **85**, which then reacts with the phosphine reagent in an

intramolecular aza-Wittig reaction, leading to the desired benzo[*d*]isothiazole **86**. The optimised system uses isopentyl nitrile (*i*-pentylONO) as the nitrogen source and the triphenylphosphine derivative $EtPPh_2$ as the phosphine substrate. Several solvents, such as dioxane, DMF, DCM and toluene, were efficient for the synthesis of benzo[*d*]isothiazoles, yet THF furnished the desired product in the highest yield. To prevent the decomposition of the nitroso compounds, the reactions were carried out at a temperature of 0 °C. Using these optimised conditions, a small library of benzo[*d*]isothiazoles was synthesised, possessing alkyl or aryl moieties at the 3-position.



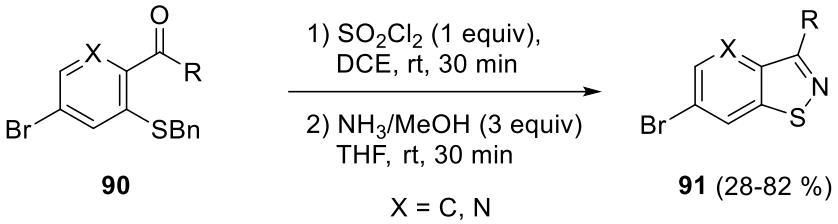
Scheme 29. Formation of benzo[*d*]isothiazoles from *ortho*-mercaptoacetophenones, using isopentyl nitrile. [82]

Dang and co-workers reported a synthesis of benzo[*d*]isothiazoles **88** based on a double lithiation strategy (Scheme 30).[83] Within this work, an indirect method, including trilithium thioanisole complex **89**, and a direct method, were developed. In the indirect methodology, the initial treatment of thioanisole **87** with an organolithium reagent and tetramethylethylenediamine (TMEDA) in hexane at a temperature of 65 °C leads to the formation of trilithium thioanisole dimer **89** with a yield of 95%. Subsequent addition of various nitriles at room temperature in methyl *tert*-butyl ether (MTBE) affords the corresponding benzo[*d*]isothiazoles **88** in yields of up to 74%. The direct synthesis proceeds under milder conditions, starting from thioanisoles **87** being treated with *n*-BuLi and TMEDA in MTBE, resulting in a lithiated species which is subsequently trapped by the corresponding nitrile. The desired products are obtained with comparable yields, reaching a maximum of 74%.



Scheme 30. Direct and indirect formation of benzo[*d*]isothiazoles from thioanisoles, using a double-lithiation strategy. [83]

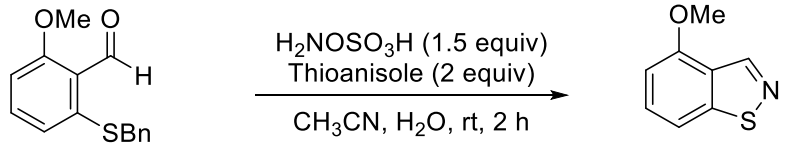
Following a procedure described in 1993,[84] several novel structures featuring benzo[*d*]isothiazole as a central scaffold were prepared (Scheme 31).[8] The ring closure of benzylthio derivatives **90** bearing a carbonyl functionality proceeds using sulfuryl chloride (SO_2Cl_2) oxidant and ammonia (NH_3) as the source of nitrogen. The resulting benzo[*d*]isothiazoles **91** were formed in yields up to 82% and further functionalized. 6-Bromo-3-(trifluoromethyl)benzo[*d*]isothiazole, being a rare example of a trifluoromethyl group installed at the 3-position of the benzo[*d*]isothiazole scaffold, was also obtained within the scope of the reaction, albeit in a low yield of 5%.



90 **91** (28-82 %)

Scheme 31. Formation of benzo[*d*]isothiazoles from *S*-(2-acetyl-5-bromophenyl) benzothioates, using sulfuryl chloride and ammonia. [8]

4-Methoxybenzo[*d*]isothiazole was obtained as part of the research conducted by Kawakita and colleagues (Scheme 32).[85] This stand-alone example was prepared using 2-(benzylthio)-6-methoxybenzaldehyde **92** as the substrate. Treating the latter with hydroxylamine *O*-sulfonic acid in the presence of thioanisole in aqueous acetonitrile affords the cyclized product **93**. A similar aldehyde-containing starting material was used as an isolated example of benzo[*d*]isothiazole assembly in another report, in which nitrogen was introduced by means of hydroxylammonium chloride.[86]



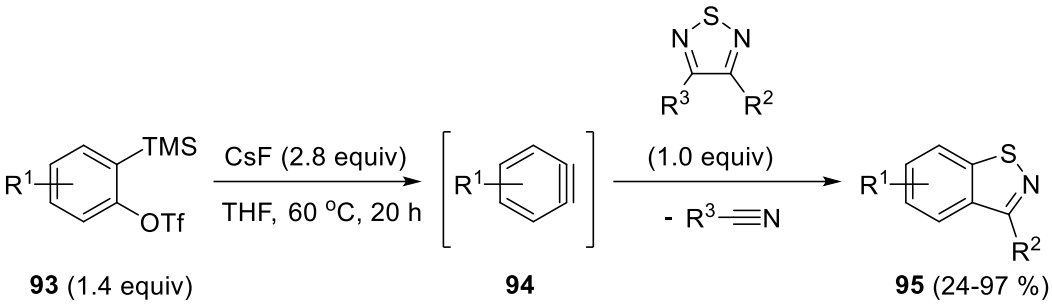
92 **93** (85 %)

Scheme 32. Formation of benzo[*d*]isothiazole from 2-(benzylthio)-6-methoxybenzaldehyde, using hydroxylamine *O*-sulfonic acid. [85]

5. Synthesis of Benzo[*d*]isothiazoles from Nitrogen and Sulfur Free Aromatics

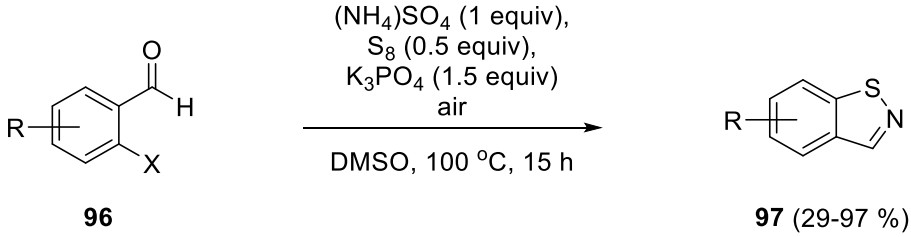
In 2015, Willis *et al*. reported a transition-metal-free synthesis of benzo[*d*]isothiazoles **95** by a cycloaddition reaction between benzyne **94** and an intermediate formed from 1,2,5-thiadiazoles **93** (Scheme 33).[87] Benzynes are generated *in situ* from the corresponding 2-(trimethylsilyl)aryl triflates **93** using cesium fluoride. By varying the benzyne precursor and the thiadiazole component, a diverse range of benzo[*d*]isothiazoles **95** was synthesised with yields from 24 to 97%, effectively incorporating electron-withdrawing, -donating and -neutral substituents. This synthetic strategy works especially well for symmetrical benzyne precursors and thiadiazoles. When symmetrical benzyne precursors and unsymmetrical 3-dialkylamino-4-hydroxythiadiazoles were used the 3-amino-substituted benzo[*d*]isothiazoles were selectively formed. In contrast, using methoxy- instead of

hydroxy-substituted thiadiazoles leads to an unselective outcome. Similarly, *in situ* generated benzyne can be used for the synthesis of enantiopure cyclic sulfoximines (1-(*tert*-butyl)benzo[*d*]isothiazole 1-oxides).[88]



Scheme 33. Formation of benzo[*d*]isothiazoles from 2-(trimethylsilyl)aryl triflates, using cesium fluoride. [87]

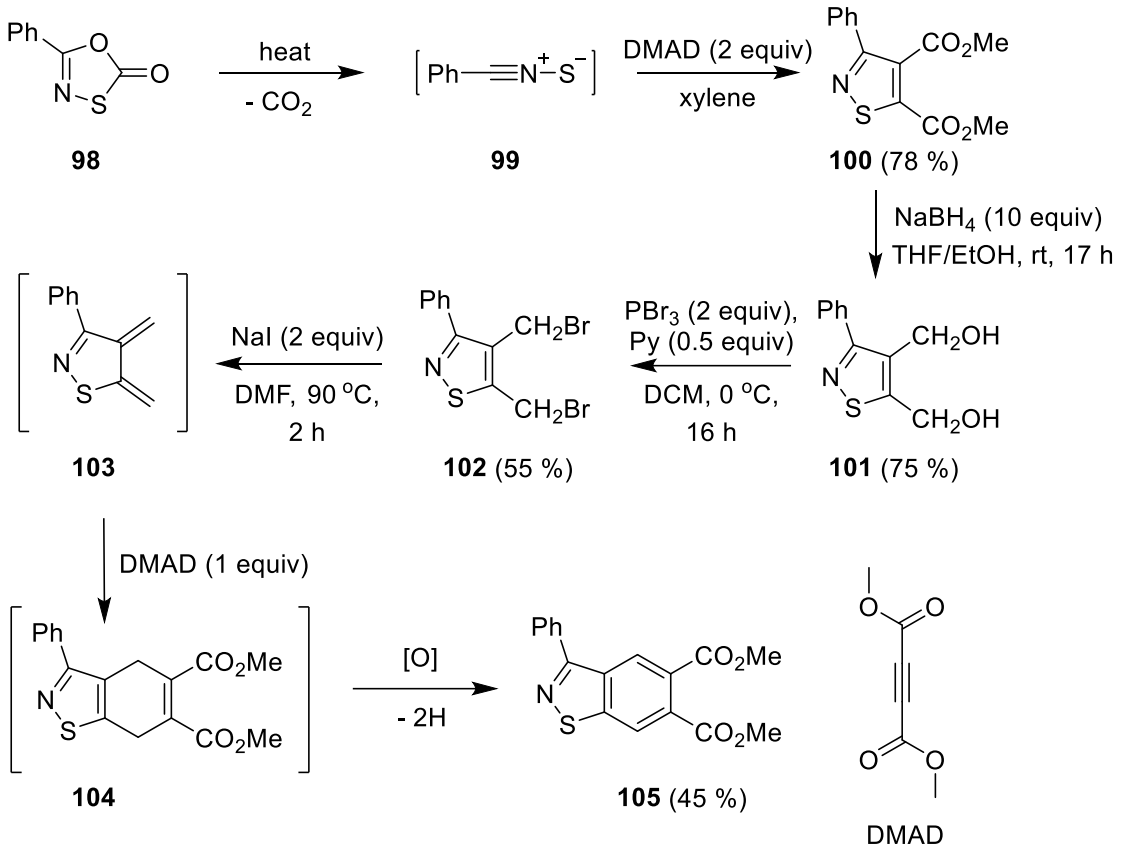
Recently, a simple, environmentally benign, synthesis of benzo[*d*]isothiazoles **97** from readily-available *ortho*-functionalized benzaldehydes **96** was reported by Wang and co-workers (Scheme 34).[89] This method employs inorganic and inexpensive ammonium sulfate ($(NH_4)_2SO_4$) and elemental sulfur, avoiding the use of transition metals. The reaction exhibits tolerance against aerobic conditions and can be effectively scaled up, as exemplified by the large-scale synthesis of benclothiaz (a pesticide) on a 5-mmol scale. Six benzo[*d*]isothiazoles were synthesised using this procedure with yields of up to 54%. The versatility of this method extends to the synthesis of pyridine- and quinoline-fused isothiazoles with overall yields ranging from 29 to 97%.



Scheme 34. Formation of benzo[*d*]isothiazoles from *ortho*-functionalized benzaldehydes, using potassium phosphate. [89]

6. Synthesis of Benzo[d]isothiazoles from an Isothiazole Scaffold

An alternative way to obtain benzo[*d*]isothiazoles is to assemble the phenyl ring onto a preformed isothiazole at a late stage. This approach was described by Ross *et al*., using nitrile sulfide chemistry and Diels-Alder reactions to ultimately prepare a decorated benzo[*d*]isothiazole scaffold (Scheme 35).[90] Dimethyl 3-phenyl-benzo[*d*]isothiazole-5,6-dicarboxylate **105** is obtained starting from benzonitrile sulfide **99**, a reactive species generated *via* thermal decarboxylation from 5-substituted-1,3,4-oxathiazol-2-one **98**. The reaction proceeds further with the [3+2]-cycloaddition between the generated nitrile sulfide and the triple bond of dimethyl acetylenedicarboxylate (DMAD). From this diester **100**, the intermediate isothiazole *o*-quinodimethane **103** is generated by reduction, bromination and bromine elimination, and the highly reactive diene is immediately trapped by DMAD as its Diels-Alder adduct **104**, and then oxidatively aromatized. Using different dienophiles for the final Diels-Alder step, several aliphatic structures were assembled on the isothiazole core.



Scheme 35. Formation of benzo[*d*]isothiazole using a multi-step procedure. [90]

7. Conclusions

Since 2010, an increased amount of research has been conducted in the field of benzo[*d*]isothiazole synthesis. Although some procedures were inspired by previously developed methods, a significant number of novel synthetic pathways have been reported. In this review, we classified these pathways into five categories, based on the substrates used for benzo[*d*]isothiazole assembly. The first four sections are dedicated to starting materials with a phenyl core and are divided based on the presence of the required heteroatoms in the substrate (both sulfur and nitrogen, only nitrogen, only sulfur, none of those). The last part included a rather rare example of a method, where the aryl moiety gets assembled starting from the existing isothiazole structure. Each chapter, where applicable, was divided into two subchapters of benzo[*d*]isothiazol-3(2*H*)-ones and benzo[*d*]isothiazoles synthesis. This decision was driven by the fact that, for the synthesis of benzo[*d*]isothiazol-3(2*H*)-ones, the carbonyl (amide) precursors were used with the substituent attached to the nitrogen atom. This particular placement of the substituent on the nitrogen of the isothiazole ring is possible due to the tautomerization of 3-hydroxy benzo[*d*]isothiazole to benzo[*d*]isothiazol-3(2*H*)-one. Therefore, benzo[*d*]isothiazol-3(2*H*)-ones possess a unique substitution pattern in comparison to the classic benzo[*d*]isothiazoles.

From this review, it is clear that the field of benzo[*d*]isothiazole synthesis has witnessed a remarkable expansion in recent decades. Various protocols were developed, however, most of them use at least a catalytic amount of transition metals to drive the reaction to completion. Furthermore, elevated temperatures were needed for particular examples, which comes at a high price of energy costs. On the other hand, some research focused on the development of greener and more sustainable methods with the production of only benign by-products.

For instance, electrochemical and photochemical approaches were developed, and several procedures that used metal catalysts also included recyclability studies. Overall, a broad variation of starting materials was utilised for benzo[*d*]isothiazole synthesis, the structures of which were predominantly aromatic-based. The rare examples of heteroaromatic substrates being employed often gave a rather low yield. For some methods, sulfur could be replaced by selenium, affording benzo[*d*][1,2]selenazoles, in high yields. Most of the fully decorated benzo[*d*]isothiazoles were prepared from starting materials carrying a fixed substitution pattern, which significantly hinders the post-functionalization in later steps of the synthetic sequence. The obtained benzo[*d*]isothiazoles and their variations were broadly employed in fields of medicinal chemistry, catalysis, peptide synthesis and chiral-compound preparation. Considering this, we expect more protocols for benzo[*d*]isothiazole synthesis to be developed in the near future, with a higher emphasis on the sustainability of procedures and more in-depth applications. This scaffold remains interesting for a wide array of purposes, and a broader library of compounds, including heterocyclic examples, would only expand its potential applications.

Acknowledgments

This research was supported by the Research Foundation Flanders (FWO) through the strategic basic research grant (1S04023N) to Y.I.

Data availability

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

ORCID

Yulia Ivanova https://orcid.org/0000-0002-6131-5693
Marin Smoljo https://orcid.org/0009-0000-2973-9333
Steven De Jonghe http://orcid.org/0000-0002-3872-6558
Wim Dehaen http://orcid.org/0000-0002-9597-0629

References

1. Matzen, L.; Engesgaard, A.; Ebert, B.; Didriksen, M.; Frølund, B.; Krogsgaard-Larsen, P.; Jaroszewski, J. W. J Med Chem **1997**, *40*, 520. https://doi.org/DOI10.1021/JM9607212
2. Fisher, M. J.; Backer, R. T.; Barth, V. N.; Garbison, K. E.; Gruber, J. M.; Heinz, B. A.; Iyengar, S.; Hollinshead, S. P.; Kingston, A.; Kuklish, S. L.; Li, L.; Nisenbaum, E. S.; Peters, S. C.; Phebus, L.; Simmons, R. M. A.; Van Der Aar, E. Bioorg Med Chem Lett **2012**, *22*, 2514. https://doi.org/10.1016/J.BMCL.2012.02.003
3. Larson, G.; Yan, S.; Chen, H.; Rong, F.; Hong, Z.; Wu, J. Z. Bioorg Med Chem Lett **2007**, *17*, 172. https://doi.org/DOI:10.1016/J.BMCL.2006.09.067
4. Zhang, X.; Cai, C.; Sui, Z.; Macielag, M.; Wang, Y.; Yan, W.; Suckow, A.; Hua, H.; Bell, A.; Haug, P.; Clapper, W.; Jenkinson, C.; Gunnet, J.; Leonard, J.; Murray, W. V. ACS Med Chem Lett **2017**, *8*, 947. https://doi.org/10.1021/ACSMEDCHEMLETT.7B00233

5. Raap, H.; Micetich, R. G. J Med Chem **1968**, *11*, 70.

https://doi.org/10.1021/JM00307A015

6. Vicini, P.; Incerti, M.; La Colla, P.; Loddo, R. Eur J Med Chem **2009**, *44*, 1801.

https://doi.org/10.1016/J.EJMECH.2008.05.030

7. Geronikaki, A.; Vicini, P.; Dabarakis, N.; Lagunin, A.; Poroikov, V.; Dearden, J.; Modarresi, H.; Hewitt, M.; Theophilidis, G. Eur J Med Chem **2009**, *44*, 473.

https://doi.org/10.1016/J.EJMECH.2008.04.006

8. Bollinger, S. R.; Engers, D. W.; Panarese, J. D.; West, M.; Engers, J. L.; Loch, M. T.; Rodriguez, A. L.; Blobaum, A. L.; Jones, C. K.; Thompson Gray, A.; Conn, P. J.; Lindsley, C. W.; Niswender, C. M.; Hopkins, C. R. J Med Chem **2019**, *62*, 342.

https://doi.org/10.1021/ACS.JMEDCHEM.8B00994

9. Gao, Y.; Wang, H.; Shen, L.; Xu, H.; Deng, M.; Cheng, M.; Wang, J. Bioorg Chem **2022**, *123*, 105769.

https://doi.org/10.1016/J.BIOORG.2022.105769

10. Zhou, H.; Danger, D. P.; Dock, S. T.; Hawley, L.; Roller, S. G.; Smith, C. D.; Handlon, A. L. ACS Med Chem Lett **2010**, *1*, 19.

https://doi.org/10.1021/ML900010B

11. Rosa, A. R.; Franco, C.; Torrent, C.; Comes, M.; Cruz, N.; Horga, G.; Benabarre, A.; Vieta, E. CNS Neurosci Ther **2008**, *14*, 278.

https://doi.org/10.1111/J.1755-5949.2008.00056.X

12. George, M.; Amrutheshwar, R.; Rajkumar, R. P.; Kattimani, S.; Dkhar, S. A. Eur J Clin Pharmacol **2013**, *69*, 1497.

https://doi.org/10.1007/S00228-013-1498-4

13. Okugawa, G.; Kato, M.; Wakeno, M.; Koh, J.; Morikawa, M.; Matsumoto, N.; Shinosaki, K.; Yoneda, H.; Kishimoto, T.; Kinoshita, T. Psychiatry Clin Neurosci **2009**, *63*, 322.

https://doi.org/10.1111/J.1440-1819.2009.01947.X

14. Yevich, J. P.; New, J. S.; Smith, D. W.; Lobeck, W. G.; Catt, J. D.; Minielli, J. L.; Eison, M. S.; Taylor, D. P.; Riblet, L. A.; Temple, D. L. J Med Chem **1986**, *29*, 359.

https://doi.org/10.1021/JM00153A010

15. Price, K. E.; Armstrong, C. M.; Imlay, L. S.; Hodge, D. M.; Pidathala, C.; Roberts, N. J.; Park, J.; Mikati, M.; Sharma, R.; Lawrenson, A. S.; Tolia, N. H.; Berry, N. G.; O'Neill, P. M.; John, A. R. O. Scientific Reports 2016 6:1 **2016**, *6*, 1.

https://doi.org/10.1038/srep36777

16. Smith, S. M. E.; Min, J.; Ganesh, T.; Diebold, B.; Kawahara, T.; Zhu, Y.; McCoy, J.; Sun, A.; Snyder, J. P.; Fu, H.; Du, Y.; Lewis, I.; Lambeth, J. D. Chem Biol **2012**, *19*, 752.

https://doi.org/10.1016/J.CHEMBIOL.2012.04.015

17. Bukya, H.; Nayani, K.; Gangireddy, P.; Mainkar, P. S. European J Org Chem **2020**, *2020*, 5358.

https://doi.org/10.1002/EJOC.202000722

18. Song, W.; Zhuang, J.; Zhang, N.; Ren, X.; Xu, W.; Guo, M.; Diao, X.; Liu, C.; Jin, J.; Wu, D.; Zhang, Y. Bioorg Med Chem **2023**, *77*.

https://doi.org/10.1016/j.bmc.2022.117041

19. Yoshioka, K.; Nakashita, H.; Klessig, D. F.; Yamaguchi, I. The Plant Journal **2008**, *25*, 149.

https://doi.org/10.1111/j.1365-313x.2001.00952.x

20. de Vicente, J.; Hendricks, R. T.; Smith, D. B.; Fell, J. B.; Fischer, J.; Spencer, S. R.; Stengel, P. J.; Mohr, P.; Robinson, J. E.; Blake, J. F.; Hilgenkamp, R. K.; Yee, C.; Adjabeng, G.; Elworthy, T. R.; Li, J.; Wang, B.; Bamberg, J. T.; Harris, S. F.; Wong, A.; Leveque, V. J. P.; Najera, I.; Pogam, S. Le; Rajyaguru, S.; Ao-Ieong, G.; Alexandrova, L.; Larrabee, S.; Brandl, M.; Briggs, A.; Sukhtankar, S.; Farrell, R. Bioorg Med Chem Lett **2009**, *19*, 5652. https://doi.org/10.1016/j.bmcl.2009.08.022

21. Wrobel, J.; Dietrich, A.; Woolson, S. A.; Millen, J.; Mccaleb, M.; Harrison, M. C.; Hohman, T. C.; Sredy, J.; Sullivan, D. *Novel Spirosuccinimides with Incorporated Isoindolone and Benzisothiazole 1,1-Dioxide Moieties as Aldose Reductase Inhibitors and Antihyperglycemic Agents*; **1992**; Vol. 35.

22. Nakashita, H.; Yoshioka, K.; Yasuda, M.; Nitta, T.; Arai, Y.; Yoshida, S.; Yamaguchi, I. Physiol Mol Plant Pathol **2002**, *61*, 197.

https://doi.org/10.1006/pmpp.2002.0426

23. Zhang, S.; Li, L.; Hu, Y.; Zha, Z.; Wang, Z.; Loh, T. P. Org Lett **2015**, *17*, 1050.

https://doi.org/10.1021/acs.orglett.5b00196

24. Hatchard, W. R. *HATCHARD VOL. 29 The Synthesis of Isothiazoles. I. 3,5-Dichloro-4-isothiazolecarbonitrile and Its Derivatives*.

25. Mahmood, A. A. R.; Al-Juboori, S. B. Ibn AL- Haitham Journal For Pure and Applied Sciences **2020**, *33*, 43.

https://doi.org/10.30526/33.2.2442

26. Seth, S. Antiinflamm Antiallergy Agents Med Chem **2015**, *14*, 98.

https://doi.org/10.2174/1871523014666150528110703

27. Yadav, K. P.; Rahman, M. A.; Nishad, S.; Maurya, S. K.; Anas, M.; Mujahid, M. Intelligent Pharmacy **2023**, *1*, 122.

https://doi.org/10.1016/J.IPHA.2023.06.001

28. Lawson, A. J. Phosphorus and Sulfur and the Related Elements **1982**, *12*, 357.

https://doi.org/10.1080/03086648208078969

29. Creed, T.; Leardini, R.; McNab, H.; Nanni, D.; Nicolson, I. S.; Reed, D. J Chem Soc Perkin 1 **2001**, 1079.

https://doi.org/10.1039/b009844m

30. Brown, D. W.; Sainsbury, M. In *Category 2, Hetarenes and Related Ring Systems*; Schaumann, E., Ed.; **2002**.

https://doi.org/10.1055/sos-sd-011-00742

31. Nutaitis, C. F. Gribble, G. W., Ed.; Springer Berlin Heidelberg: Berlin, Heidelberg, **2012**; 329.

https://doi.org/10.1007/7081_2012_77

32. Song, W.; Zhuang, J.; Zhang, N.; Ren, X.; Xu, W.; Guo, M.; Diao, X.; Liu, C.; Jin, J.; Wu, D.; Zhang, Y. Bioorg Med Chem **2023**, *77*, 117041.

https://doi.org/10.1016/J.BMC.2022.117041

33. Mulina, O. M.; Ilovaisky, A. I.; Terent'ev, A. O. European J Org Chem **2018**, *2018*, 4648.

https://doi.org/10.1002/EJOC.201800838

34. De Oliveira Silva, A.; McQuade, J.; Szostak, M. Adv Synth Catal **2019**, *361*, 3050.

https://doi.org/10.1002/ADSC.20190007 .

35. Wang, Z.; Kuninobu, Y.; Kanai, M. Journal of Organic Chemistry **2013**, *78*, 7337.

https://doi.org/10.1021/JO401056G

36. Yang, L.; Song, L.; Tang, S.; Li, L.; Li, H.; Yuan, B.; Yang, G. European J Org Chem **2019**, *2019*, 1281.

https://doi.org/10.1002/EJOC.201801642

37. Dou, Y.; Huang, X.; Wang, H.; Yang, L.; Li, H.; Yuan, B.; Yang, G. Green Chemistry **2017**, *19*, 2491.

https://doi.org/10.1039/C7GC00401J

38. Hsieh, C. C.; Liu, Y. C.; Tseng, M. C.; Chiang, M. H.; Horng, Y. C. Dalton Transactions **2019**, *48*, 379.

https://doi.org/10.1039/C8DT04491K

39. Hsieh, C. C.; Li, C. Y.; Chiang, M. H.; Horng, Y. C. Chemical Communications **2022**, *58*, 12943.

https://doi.org/10.1039/D2CC05375F

40. Yu, T. Q.; Hou, Y. S.; Jiang, Y.; Xu, W. X.; Shi, T.; Wu, X.; Zhang, J. C.; He, D.; Wang, Z. Tetrahedron Lett **2017**, *58*, 2084.

https://doi.org/10.1016/J.TETLET.2017.03.065

41. Zhulenkovs, D.; Rudevica, Z.; Jaudzems, K.; Turks, M.; Leonchiks, A. Bioorg Med Chem **2014**, *22*, 5988.

https://doi.org/10.1016/J.BMC.2014.09.011

42. Dou, D.; Alex, D.; Du, B.; Tiew, K. C.; Aravapalli, S.; Mandadapu, S. R.; Calderone, R.; Groutas, W. C. Bioorg Med Chem **2011**, *19*, 5782.

https://doi.org/10.1016/J.BMC.2011.08.029

43. Lai, H.; Dou, D.; Aravapalli, S.; Teramoto, T.; Lushington, G. H.; Mwania, T. M.; Alliston, K. R.; Eichhorn, D. M.; Padmanabhan, R.; Groutas, W. C. Bioorg Med Chem **2013**, *21*, 102.

https://doi.org/10.1016/J.BMC.2012.10.058

44. Zhong, Q.; Xiong, Z.; Sheng, S.; Chen, J. Tetrahedron Lett **2021**, *80*, 153323.

https://doi.org/10.1016/J.TETLET.2021.153323

45. Nascimento, V.; Cordeiro, P. S.; Arca, M.; Marini, F.; Sancineto, L.; Braga, A. L.; Lippolis, V.; Iwaoka, M.; Santi, C. New Journal of Chemistry **2020**, *44*, 9444.

https://doi.org/10.1039/D0NJ01605E

46. Jin, W. Bin; Xu, C.; Cheung, Q.; Gao, W.; Zeng, P.; Liu, J.; Chan, E. W. C.; Leung, Y. C.; Chan, T. H.; Wong, K. Y.; Chen, S.; Chan, K. F. Bioorg Chem **2020**, *100*, 103873.

https://doi.org/10.1016/J.BIOORG.2020.103873

47. Kamigata, N.; Hashimoto, S.; Kobayashi, M. Org Prep Proced Int **1983**, *15*, 315.

https://doi.org/10.1080/00304948309356506

48. Yang, K.; Zhang, H.; Niu, B.; Tang, T.; Ge, H. European J Org Chem **2018**, *2018*, 5520.

DOI:10.1002/EJOC.201801090

49. Nyffeler, P. T.; Durón, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C. H. Angewandte Chemie International Edition **2005**, *44*, 192.

https://doi.org/10.1002/ANIE.200400648

50. Stavber, S. Molecules 2011, Vol. 16, Pages 6432-6464 **2011**, *16*, 6432.

https://doi.org/10.3390/MOLECULES16086432

51. Dai, S.; Yang, K.; Luo, Y.; Xu, Z.; Li, Z.; Li, Z.; Li, B.; Sun, X. Organic Chemistry Frontiers **2022**, *9*, 4016.

https://doi.org/10.1039/D2QO00663D

52. Jorgensen, W. L.; Trofimov, A.; Du, X.; Hare, A. A.; Leng, L.; Bucala, R. Bioorg Med Chem Lett **2011**, *21*, 4545.

https://doi.org/10.1016/J.BMCL.2011.05.127

53. Pinna, G.; Bellucci, M. C.; Malpezzi, L.; Pisani, L.; Superchi, S.; Volonterio, A.; Zanda, M. Tetrahedron **2011**, *67*, 5268.

https://doi.org/10.1016/J.TET.2011.05.033

54. Xu, F.; Chen, Y.; Fan, E.; Sun, Z. Org Lett **2016**, *18*, 2777.

https://doi.org/10.1021/ACS.ORGLETT.6B01338

55. Wei, J.; Sun, Z. Org Lett **2015**, *17*, 5396.

https://doi.org/10.1021/ACS.ORGLETT.5B02743

56. Yuan, H.; Sun, Z. Synlett **2019**, *30*, 1904.

https://doi.org/10.1055/S-0039-1690201

57. Cabrera-Afonso, M. J.; Cembellín, S.; Halima-Salem, A.; Berton, M.; Marzo, L.; Miloudi, A.; Maestro, M. C.; Alemán, J. Green Chemistry **2020**, *22*, 6792.

https://doi.org/10.1039/D0GC02618B

58. Garlapati, K. K.; Srinivasu, N.; Kumar, K. S.; Ganta, R. K. Russian Journal of Organic Chemistry **2022**, *58*, 1534.

https://doi.org/10.1134/S1070428022100220

59. Bhakuni, B. S.; Balkrishna, S. J.; Kumar, A.; Kumar, S. Tetrahedron Lett **2012**, *53*, 1354.

https://doi.org/10.1016/J.TETLET.2012.01.003

60. Balkrishna, S. J.; Bhakuni, B. S.; Chopra, D.; Kumar, S. Org Lett **2010**, *12*, 5394.

https://doi.org/10.1021/OL102027J

61. Krasikova, V.; Katkevics, M. Chem Heterocycl Compd (N Y) **2013**, *48*, 1684.

https://doi.org/10.1007/S10593-013-1193-5

62. Paul, R.; Punniyamurthy, T. RSC Adv **2012**, *2*, 7057.

https://doi.org/10.1039/C2RA20724A

63. Chen, F. J.; Liao, G.; Li, X.; Wu, J.; Shi, B. F. Org Lett **2014**, *16*, 5644.

https://doi.org/10.1021/OL5027156

64. Wang, F.; Chen, C.; Deng, G.; Xi, C. Journal of Organic Chemistry **2012**, *77*, 4148.

https://doi.org/10.1021/JO300250X

65. Li, T.; Yang, L.; Ni, K.; Shi, Z.; Li, F.; Chen, D. Org Biomol Chem **2016**, *14*, 6297.

https://doi.org/10.1039/C6OB00819D

66. Guo, J. R.; Gong, J. F.; Song, M. P. Org Biomol Chem **2019**, *17*, 5029.

https://doi.org/10.1039/C9OB00449A

67. Liu, S. L.; Li, X. H.; Shi, T. H.; Yang, G. C.; Wang, H. L.; Gong, J. F.; Song, M. P. European J Org Chem **2017**, *2017*, 2280.

https://doi.org/10.1002/EJOC.201700147

68. Dhara, S.; Saha, M.; Das, A. R. New Journal of Chemistry **2022**, *46*, 19501.

https://doi.org/10.1039/D2NJ04326B

69. Moon, S.; Nishii, Y.; Miura, M. Org Lett **2021**, *23*, 49.

https://doi.org/10.1021/ACS.ORGLETT.0C03674

70. Wang, Q.; Xiao, F.; Huang, Z.; Mao, G.; Deng, G. J. Journal of Organic Chemistry **2023**, *88*, 1963.

https://doi.org/10.1021/ACS.JOC.2C02088

71. Xie, H.; Li, G.; Zhang, F.; Xiao, F.; Deng, G. J. Green Chemistry **2018**, *20*, 827.

https://doi.org/10.1039/C7GC03599C

72. Wu, Q.; Deng, Z.; Xie, D.; Liu, Y.; Yang, Q.; Fu, Y.; Peng, Y. Tetrahedron **2022**, *124*, 132911.

https://doi.org/10.1016/J.TET.2022.132911

73. Xu, R.; Xiao, G.; Li, Y.; Liu, H.; Song, Q.; Zhang, X.; Yang, Z.; Zheng, Y.; Tan, Z.; Deng, Y. Bioorg Med Chem **2018**, *26*, 1885.

https://doi.org/10.1016/J.BMC.2018.02.037

74. Yevich, J. P.; New, J. S.; Smith, D. W.; Lobeck, W. G.; Catt, J. D.; Minielli, J. L.; Eison, M. S.; Taylor, D. P.; Riblet, L. A.; Temple, D. L. J Med Chem **1986**, *29*, 359.

https://doi.org/10.1021/JM00153A010

75. Castelli, R.; Scalvini, L.; Vacondio, F.; Lodola, A.; Anselmi, M.; Vezzosi, S.; Carmi, C.; Bassi, M.; Ferlenghi, F.; Rivara, S.; Møller, I. R.; Rand, K. D.; Daglian, J.; Wei, D.; Dotsey, E. Y.; Ahmed, F.; Jung, K. M.; Stella, N.; Singh, S.; Mor, M.; Piomelli, D. J Med Chem **2020**, *63*, 1261.

https://doi.org/10.1021/ACS.JMEDCHEM.9B01679

76. Correa, A.; Tellitu, I.; Domínguez, E.; SanMartin, R. Org Lett **2006**, *8*, 4811.

https://doi.org/10.1021/OL061867Q

77. Abdul-Hay, S. O.; Bannister, T. D.; Wang, H.; Cameron, M. D.; Caulfield, T. R.; Masson, A.; Bertrand, J.; Howard, E. A.; McGuire, M. P.; Crisafulli, U.; Rosenberry, T. R.; Topper, C. L.; Thompson, C. R.; Schürer, S. C.; Madoux, F.; Hodder, P.; Leissring, M. A. ACS Chem Biol **2015**, *10*, 2716.

https://doi.org/10.1021/ACSCHEMBIO.5B00334

78. Dhanya, R. P.; Sidique, S.; Sheffler, D. J.; Nickols, H. H.; Herath, A.; Yang, L.; Dahl, R.; Ardecky, R.; Semenova, S.; Markou, A.; Conn, P. J.; Cosford, N. D. P. J Med Chem **2011**, *54*, 342.

https://doi.org/10.1021/JM1012165

79. Dahl, R.; Bravo, Y.; Sharma, V.; Ichikawa, M.; Dhanya, R. P.; Hedrick, M.; Brown, B.; Rascon, J.; Vicchiarelli, M.; Mangravita-Novo, A.; Yang, L.; Stonich, D.; Su, Y.; Smith, L. H.; Sergienko, E.; Freeze, H. H.; Cosford, N. D. P. J Med Chem **2011**, *54*, 3661.

https://doi.org/10.1021/JM101401A

80. Bravo, Y.; Teriete, P.; Dhanya, R. P.; Dahl, R.; Lee, P. S.; Kiffer-Moreira, T.; Ganji, S. R.; Sergienko, E.; Smith, L. H.; Farquharson, C.; Millán, J. L.; Cosford, N. D. P. Bioorg Med Chem Lett **2014**, *24*, 4308. https://doi.org/10.1016/J.BMCL.2014.07.013

81. Shimizu, M.; Shimazaki, T.; Yoshida, T.; Ando, W.; Konakahara, T. Tetrahedron **2012**, *68*, 3932.

https://doi.org/10.1016/J.TET.2012.03.094

82. Devarie-Baez, N. O.; Xian, M. Org Lett **2010**, *12*, 752.

https://doi.org/10.1021/OL9028447

83. Zhu, R.; Liu, Z.; Chen, J.; Xiong, X.; Wang, Y.; Huang, L.; Bai, J.; Dang, Y.; Huang, J. Org Lett **2018**, *20*, 3161.

https://doi.org/10.1021/ACS.ORGLETT.8B00850

84. Fink, D. M.; Strupczewski, J. T. Tetrahedron Lett **1993**, *34*, 6525.

https://doi.org/10.1016/0040-4039(93)88095-Z

85. Kawakita, Y.; Banno, H.; Ohashi, T.; Tamura, T.; Yusa, T.; Nakayama, A.; Miki, H.; Iwata, H.; Kamiguchi, H.; Tanaka, T.; Habuka, N.; Sogabe, S.; Ohta, Y.; Ishikawa, T. J Med Chem **2012**, *55*, 3975. https://doi.org/10.1021/JM300185P

86. Blunt, C. E.; Torcuk, C.; Liu, Y.; Lewis, W.; Siegel, D.; Ross, D.; Moody, C. J. Angewandte Chemie International Edition **2015**, *54*, 8740.

https://doi.org/10.1002/ANIE.201503323

87. Chen, Y.; Willis, M. C. Org Lett **2015**, *17*, 4786.

https://doi.org/10.1021/ACS.ORGLETT.5B02347

88. Ye, W.; Zhang, L.; Ni, C.; Rong, J.; Hu, J. Chemical Communications **2014**, *50*, 10596.

https://doi.org/10.1039/C4CC05042H

89. Wang, M.; Meng, X.; Cai, C.; Wang, L.; Gong, H. Green Synthesis and Catalysis **2022**, *3*, 168.

https://doi.org/10.1016/J.GRESC.2022.03.005

90. Ross, J. F.; Delipala, C.; Watson, M. C.; Crosby, J.; Paton, R. M. Arkivoc **2013**, *2013*, 372.

https://doi.org/10.3998/ARK.5550190

Authors' Biographies

Yulia Ivanova was born in Moscow, Russia. She received her BEng degree in Chemical Engineering at the Mendeleev University of Chemical Technology in 2020. Two years later, she obtained her MSc degree in Chemistry at the KU Leuven with a specialization in organic chemistry. During her Master's thesis, she worked on the development of novel CXCR4 antagonists under the supervision of Prof. W. Dehaen. She continued in the research group of Prof. W. Dehaen as an FWO doctoral fellow. Her current research encompasses the synthesis

of novel small heterocyclic molecules, with particular interest in methodology development and their applications in medicinal chemistry.

Marin Smoljo was born in Slavonski Brod, Croatia, in 1997. He received his Bachelor's degree in Applied Chemistry from the University of Zagreb, Croatia, in 2019. In 2023, he obtained his master's degree from the Technical University of Munich, Germany, with the specialization in organic and biological chemistry. For his master's thesis, he conducted research on the synthesis and postfunctionalization of benzoisothiazoles at KU Leuven under the supervision of Prof. Wim Dehaen (February - June 2023). His research experience revolves around organic chemistry, with emphasis on the synthesis of organic compounds and methodology development.

Steven De Jonghe received his Master's degree in Pharmaceutical Sciences from the University of Gent (Belgium) in 1996. In 2000, he obtained a Ph.D. in Pharmaceutical Sciences from the same university with a thesis entitled 'Synthesis and biological evaluation of dihydroceramide and homoceramide analogues'. He was an industrial postdoctoral fellow at Gilead Sciences (Foster City, CA, USA) and postdoctoral scientist/Industrial Research Manager at the Lab of Medicinal Chemistry of the Rega Institute at the KU Leuven (Belgium). He was also a medicinal chemist at 4AZA Bioscience, a spin-off company from KU Leuven. Currently, he is affiliated as a Research Manager at the Laboratory of Virology and Chemotherapy of the Rega Institute at the KU Leuven (Belgium), where he is involved in small molecule drug discovery targeting various kinases and chemokine GPCRs, as well as in antiviral and antitumoral drug discovery programs.

Prof. Dr. Wim Dehaen was born in Kortrijk, Belgium, in 1962. He obtained his PhD in 1988 at KU Leuven. After postdoctoral stays in Israel (1988–1990), Denmark (3 months in 1990), the UK (3 months in 1994), and the KU Leuven (Belgium) from 1990 until 1998, he became associate professor in 1998 and full professor at the latter university in 2004. To date, over 650 publications have appeared in international journals on his work on heterocyclic and supramolecular chemistry.

