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A Review on the Synthesis and Use of Benzobisthiazoles: An Important Class of Heterocycles

Ratna Mukherjee *

Department of Chemistry, Dum Dum Motijheel College, 1, Motijheel Avenue, Kolkata 700074, West Bengal, India
Email: ratna.org@gmail.com

ABSTRACT

This review emphasises on the synthesis of various benzobisthiazole derivatives both linear and angular isomers. According to the position of nitrogen and sulphur atoms in this type of heteroarene, the linear benzobisthiazole moiety has two types of skeleton whereas the angular isomer has three types. Additionally, this review enlightens the role of few benzobisthiazole derivatives in biological field. Eventually a wide variety of other uses of benzobisthiazoles and their polymers are also discussed in brief.

KEYWORDS: benzobisthiazoles, synthesis, biological activity

*Corresponding author

Dr. Ratna Mukherjee

Assistant Professor, Department of Chemistry

Dum Dum Motijheel College

1, Motijheel Avenue, Kolkata-700074, West Bengal, India

E-mail: ratna.org@gmail.com

1. INTRODUCTION

The importance of sulphur atoms in the living organisms is well documented.[1] The thiazoles constitute an important class of heterocyclic that contains one sulphur atom. The thiazoles, both substituted and annulated, are present in many natural and synthetic products possessing a wide range of pharmacological activities. These molecules display, *inter alia*, antiviral, anti-ulcer, antibacterial, antifungal, anticonvulsant, antiparkinsonian and anti-inflammatory activities. Some of them are vitamin B_1,[2,3] and the bioactive natural products are camalexins (antimicrobial) and spirobrassinins (antifungal).[4]

Some examples of thiazole containing synthetic drugs are the anticonvulsant riluzole, the antischistosomal niridazole, the anthelmintic thiabendazole, the antimicrobial sulfathiazole and the anti-HIV ritonavir.[2] The well known synthetic drugs famotidine and nizatidine (anti-ulcer)[5] also deserve special mention. Some of the synthetic thiazolylindoles also show impressive, selective COX-2 (cyclooxygenase) inhibitory activity.[6,7] The antiparkinsonian talipexole is also a well known bioactive compound.[2]

Thiazole and thiazole-annulated scaffolds are among the most prominent building blocks in chromophores with potential applications in fields such as nonlinear optics (NLO),[8-16] organic light-emitting diodes,[17] organic field-effect transistors,[18-20] dye-sensitized solar cells,[21,22] polymers,[23] liquid crystals,[24] photonucleases,[25] fluorescent dyes,[26,27] insecticides[28] and antioxidants.[29]

Among the fused thiazoles, benzothiazoles are of considerable interest as a result of their important biological and biophysical (nonlinear optical materials, molecular dyads, chemosensors)[30,31] properties. 2-Aryl and 2-heteroaryl substituted benzothiazoles have been studied as antitumor,[32] antimicrobial[33] and antifungal agents[34] and as imaging agents for β-amyloid.[35] Pertinently, 2-(4-aminophenyl)benzothiazoles are fast emerging as promising antitumor drugs.[36-38]

Among the annulated thiazoles, benzobisthiazoles have been less researched; a few reports have indicated that derivatives of these compounds show some potent biological activity. So in the present review benzobisthiazole was chosen in order to discuss about their synthesis, biological activity and other miscellaneous uses.

2. EXTANT SYNTHESES OF BENZOBISTHIAZOLES

Two types of linearly fused and three types of angularly fused benzobisthiazoles can, in principle, be formed by the fusion of the thiazole and the benzothiazole nuclei. These parent tricycle molecules are.

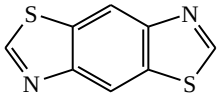
Linear benzobisthiazoles:

1) Benzo[1,2-*d*:4,5-*d'*]bisthiazoles (Type I) 2) Benzo[1,2-*d*:5,4-*d'*]bisthiazoles (Type II)

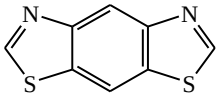
Angular benzobisthiazoles:

3) Benzo[1,2-*d*:3,4-*d*′]bisthiazoles (Type III) 4) Benzo[1,2-*d*:4,3-*d*′]bisthiazoles (Type IV)

5) Benzo[1,2-*d*:6,5-*d*′]bisthiazoles (Type V)

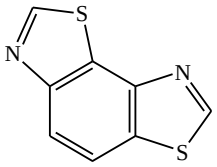


Benzo[1,2-*d*:4,5-*d*′]bisthiazole
Type I

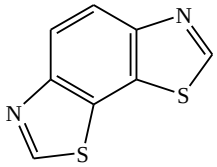


Benzo[1,2-*d*:5,4-*d*′]bisthiazole
Type II

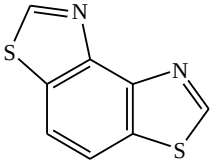
Fig. 1. Linear Benzobisthiazoles



Benzo[1,2-*d*:3,4-*d*′]bisthiazole
Type III



Benzo[1,2-*d*:4,3-*d*′]bisthiazole
Type IV



Benzo[1,2-*d*:6,5-*d*′]bisthiazole
Type V

Fig. 2. Angular Benzobisthiazoles

All the five classes of benzobisthiazoles are in fact reported in the literature. In the majority of the reported syntheses of these compounds, either *ortho*-, *meta*- and *para*-phenylenediamines or substituted 5/6/7-aminobenzothiazoles were the starting materials. The reported syntheses of the different classes of the benzobisthiazoles (Types I-V) are briefly discussed in this review.

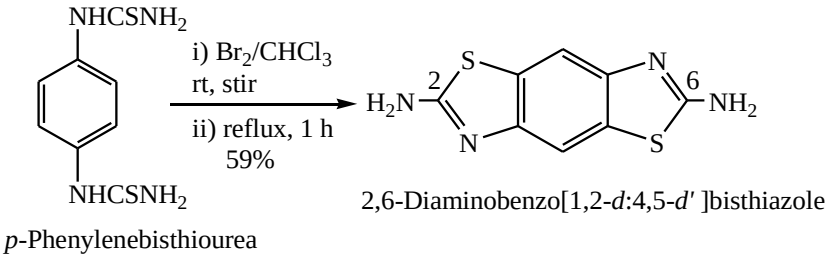
2.1 Preparation of Benzo[1,2-d:4,5-d′]bisthiazoles (Type I)

In 1903, Green and Perkin[39] first claimed to have prepared this class of linear benzobisthiazoles. Later, however, three different groups[40-42] proved that the benzobisthiazoles prepared by Green and Perkin did indeed belong to the angular [1,2-*d*:4,3-*d*′] series, i.e. Type IV. These latter workers based their conclusions on UV, IR and NMR spectroscopic analyses.

The benzobisthiazoles of Type I were prepared from *p*-phenylenebisthiourea[40] (**Scheme 1**) and 5-amino-6-nitrobenzothiazole[41] (**Scheme 2**). Type I benzobisthiazoles were also prepared by derivatisations of other benzobisthaizoles.[43] Some syntheses of Type I benzobisthiazoles are discussed here.

2.1.1 Starting from *p*-Phenylenebisthiourea[40]

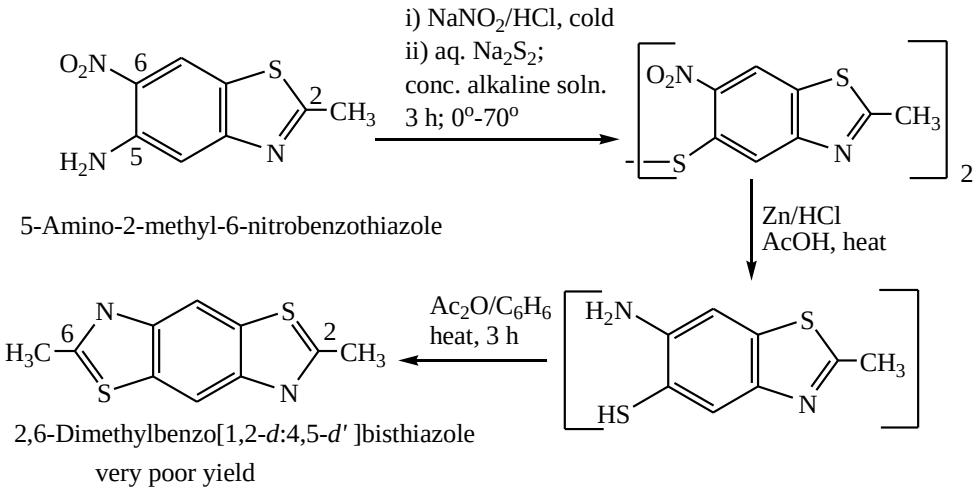
Bromine-catalysed cyclisation of thioureas derived from aromatic amines is one of the oldest (1903) methods, known as Hugershoff reaction.[44] This method was again brought to fore by Ambati et al. in 1997.[45] Application of Hugherschof protocotol to the synthesis of 2,6-diaminobenzo[1,2-*d*:4,5-*d*′]bisthiazole starting from *p*-phenylene-bisthiourea is depicted in **Scheme 1**.[40]



Scheme 1

2.1.2 Starting from 5-Amino-6-nitrobenzothiazole[41]

5-Amino-6-nitrobenzothiazole was sequentially diazotized and treated with sodium disulfide, the resulting disulfide reductively cleaved to the corresponding aminothiophenol and finally cyclised to form 2,6-dimethylbenzo[1,2-*d*:4,5-*d*′]-bisthiazole (**Scheme 2**).



Scheme 2

2.2 Preparation of Benzo[1,2-d:5,4-d′]bisthiazoles (Type II)

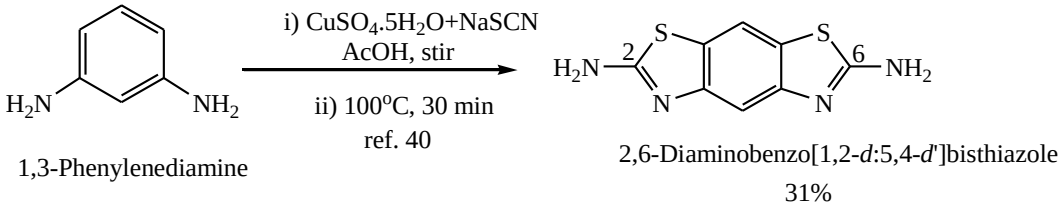
In 1922, S.R.H. Edge[46-48] claimed to have prepared 2,6-dimethyl[1,2-d:5,4-d′]-bisthiazole, i.e. a member of Type II. Subsequently, it was demonstrated[49,50] that the product was indeed the angular isomer, *viz.* 2,7-dimethylbenzo[1,2-*d*:3,4-*d*′]-bisthiazole (Type III).

Various members of Type II benzobisthiazoles were synthesised from different precursors, viz. 1,3-phenylenediamine,[43,40] 2,5-diaminobenzothiazole,[40] 1,3-dinitro-4,6-dithiocyanobenzene,[40]

dinitrothioresorcinol,[49] *m*-phenylenebisthiourea[51] and 1,3-dichloro-4,6-dinitrobenzene.[50,52] Many of these products were further derivatised, leading to the formation of a number of other members of this Type.[43] Some of these syntheses are shown in this review.

2.2.1 Starting from *m*-Phenylenediamine[43,40]

m-Phenylenediamine was made to undergo successive thiocynation and cyclisation, as depicted below, to result in the formation of 2,6-diaminobenzo[1,2-*d*:5,4-*d*′]bisthiazole (**Scheme 3**).

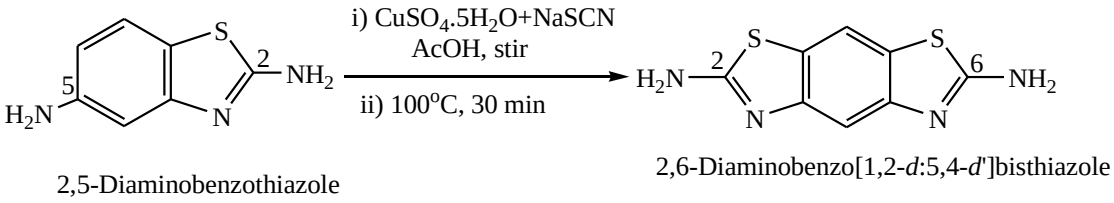


Scheme 3

The corresponding bisdiethylaminoacetyl derivative was also prepared from this benzobisthiazole.[43]

2.2.2 Starting from 2,5-Diaminobenzothiazole[40]

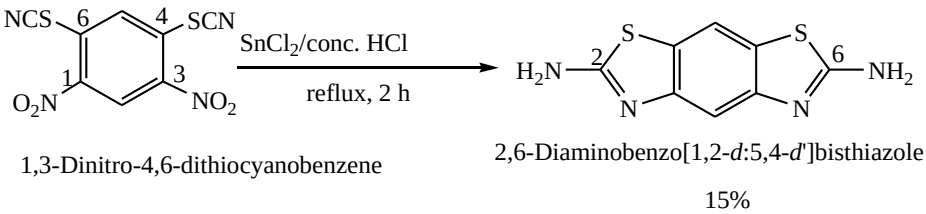
Following the same protocol as above but using 2,5-diaminobenzothiazole as the substrate, 2,6-diaminobenzo[1,2-*d*:5,4-*d*′]bisthiazole was prepared (**Scheme 4**).



Scheme 4

2.2.3 Starting from 1,3-Dinitro-4,6-dithiocyanobenzene[40]

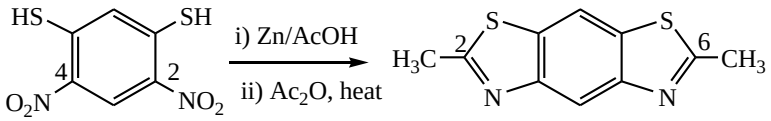
Preformed 1,3-Dinitro-4,6-dithiocyanobenzene was subjected to reductive cyclisation to furnish 2,6-diaminobenzo[1,2-*d*:5,4-*d*′]bisthiazole in a low yield (**Scheme 5**).[40] The low yield of the product renders this method of only academic interest.



Scheme 5

2.2.4 Starting from Dinitrothioresorcinol[49]

2,4-Dinitrothioresorcinol was reduced and acetylated to furnish the 2,6-dimethylbenzo[1,2-*d*:5,4-*d*′]bisthiazole in a moderate yield (**Scheme 6**).



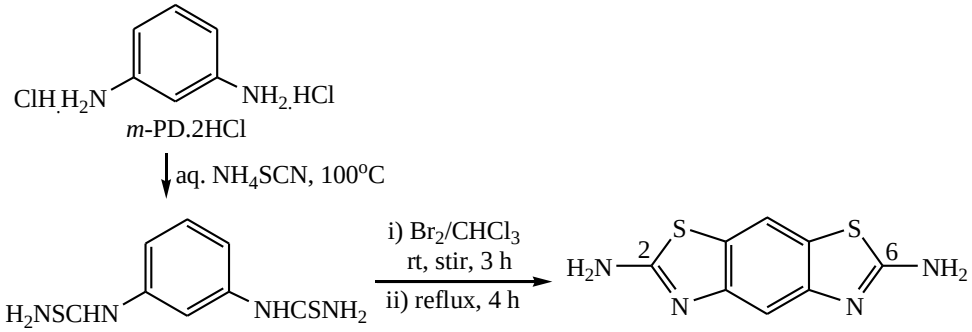
2,4-Dinitrothioresorcinol — 2,6-Dimethylbenzo[1,2-*d*:5,4-*d*']bisthiazole

50%

Scheme 6

2.2.5 Starting from *m*-Phenylenebisthiourea[51]

m-Phenylenediamine (*m*-PD) dihydrochloride on thiocyanation furnished the bisthiourea which was cyclised by Hughershoff reaction to furnish 2,6-diamino-benzo[1,2-*d*:5,4-*d*′]bisthiazole (**Scheme 7**).



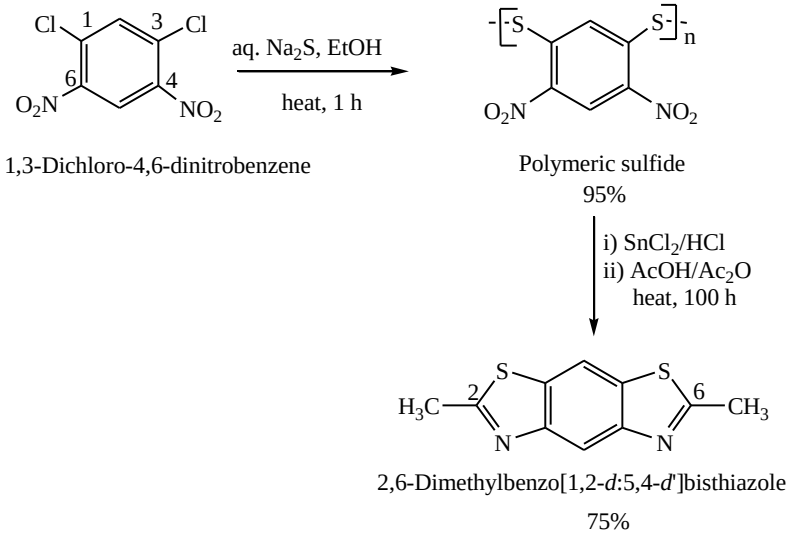
m-Phenylenebisthiourea
76%

2,6-Diaminobenzo[1,2-*d*:5,4-*d*']bisthiazole
56%

Scheme 7

2.2.6 Starting from 1,3-Dichloro-4,6-dinitrobenzene[50,52]

Various members of Type II were prepared using 1,3-dichloro-4,6-dinitro-benzene as the starting material using different methodologies.[50,52] Only one example is depicted in **Scheme 8**. Here 2,6-dimethylbenzo[1,2-*d*:5,4-*d*′]bisthiazole was prepared (**Scheme 8**).[50]



1,3-Dichloro-4,6-dinitrobenzene

Polymeric sulfide
95%

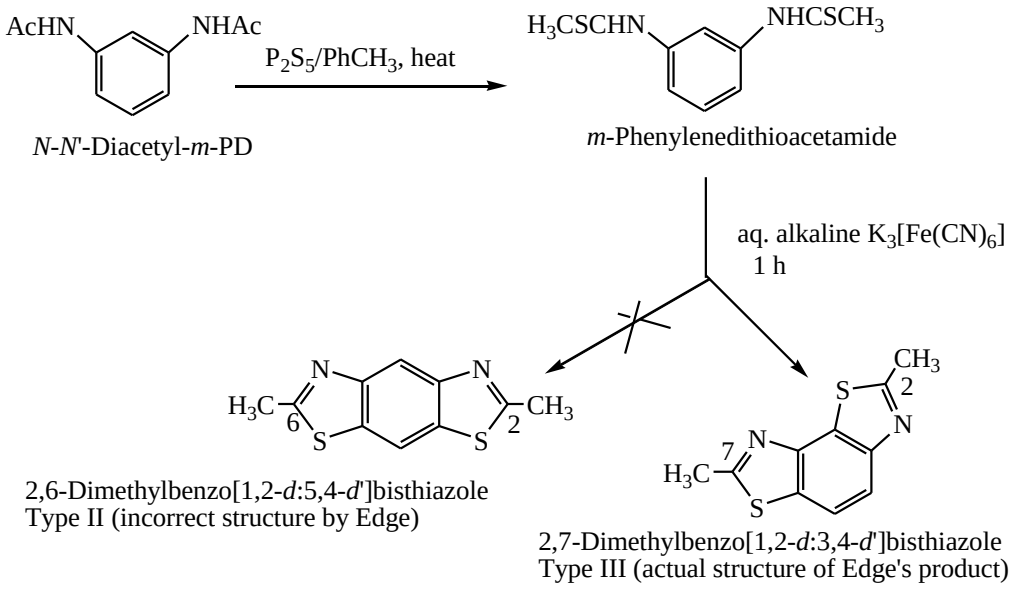
2,6-Dimethylbenzo[1,2-*d*:5,4-*d*′]bisthiazole
75%

Scheme 8

a. Preparation of Benzo[1,2-d:3,4-d′]bisthiazoles (Type III)

2.3.1 Starting from *m*-Phenylene Di Thioacetamide

An example of this type of benzobisthiazoles was first reported to be prepared by Edge[46-48] by the oxidative ring closure of *m*-phenylenedithioacetamide employing Jacobson reaction.[53] The latter is the oxidative cyclisation of aryl thioamides by aqueous alkaline potassium ferricyanide to form thiazoloarenes. But Edge wrongly identified the product as the linear molecule, 2,6-dimethylbenzo[1,2-*d*:5,4-*d*′]-bisthiazole (Type II). Later G. Grandolini et al.[49] and O. Neunhoeffer et al.[50] prepared the aforesaid molecule by two different methods (**Schemes 6** and **8**, respectively), already discussed before, and found their melting points to be different from that of Edge's compound. They, therefore, opined that the compound prepared by Edge did indeed bear the only possible alternative angular structure, viz. 2,7-dimethylbenzo[1,2-*d*:3,4-*d*′]bisthiazole (Type III). The actual experiment undertaken by Edge is represented in **Scheme 9**.



N-*N*'-Diacetyl-*m*-PD

m-Phenylenedithioacetamide

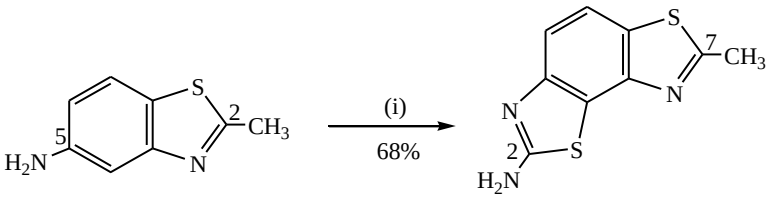
2,6-Dimethylbenzo[1,2-*d*:5,4-*d*']bisthiazole
Type II (incorrect structure by Edge)

2,7-Dimethylbenzo[1,2-*d*:3,4-*d*']bisthiazole
Type III (actual structure of Edge's product)

Scheme 9

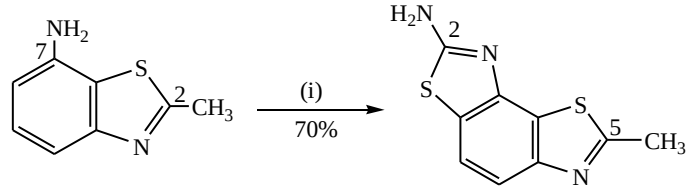
2.3.2 Starting from 5/7-Aminobenzothiazoles[54-56]

Various benzobisthiazoles of Type III were prepared from 5/7-amino- benzothiazoles.[54-56] A particular example is depicted in **Scheme 10**. Here 2-amino-7-methylbenzo[1,2-*d*:3,4-*d'*] bisthiazole and 2-amino-5-methylbenzo[1,2-*d*:3,4-*d'*] bisthiazole, were prepared in one-pot reaction.[55]



5-Amino-2-methylbenzothiazole

2-Amino-7-methylbenzo[1,2-*d*:3,4-*d*']bisthiazole



7-Amino-2-methylbenzothiazole

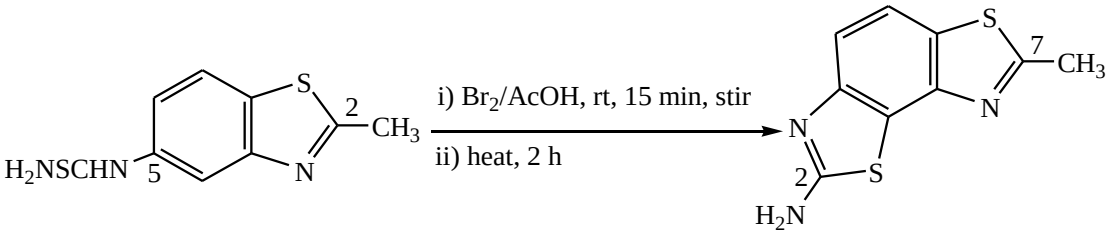
2-Amino-5-methylbenzo[1,2-*d*:3,4-*d*']bisthiazole

(i): NH_4SCN/AcOH, $O{=}C(NHCl)_2$ /AcOH, ice-cooled, 1-2 h

Scheme 10

2.3.3 Starting from 2-Methyl(benzothiazol-5-yl)thiourea[57]

2-Methyl-5-thioureidobenzothiazole was cyclised by Hugershoff reaction to furnish 2-amino-7-methylbenzo[1,2-*d*:3,4-*d'*]bisthiazole (**Scheme 11**).



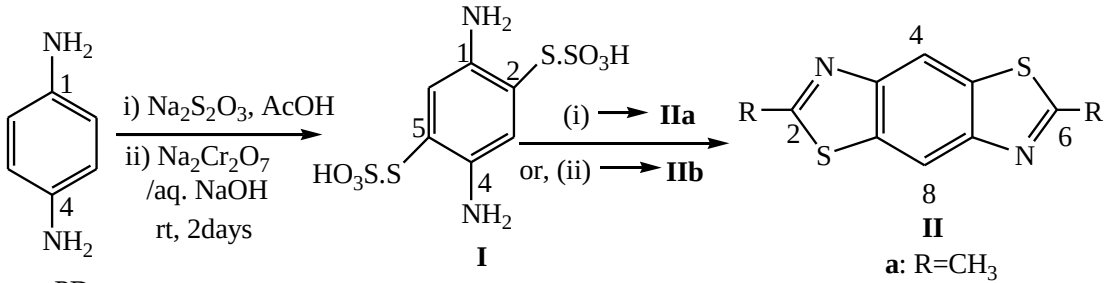
2-Methyl-5-thioureidobenzothiazole — 2-Amino-7-methylbenzo[1,2-*d*:3,4-*d*']bisthiazole

Scheme 11

2.4 Preparation of Benzo[1,2-d:4,3-d']bisthiazoles (Type IV)

2.4.1 Starting from *p*-Phenylenediamine

Green and Perkin[39] were the first to claim to have achieved the synthesis of 2,6-disubstituted benzo[1,2-*d*:4,5-*d'*]bisthiazoles (Type I) starting from *p*-phenylenediamine (*p*-PD). They thionated *p*-PD and assumed that the product was 1,4-diaminobenzene-2,5-dithiosulfonic acid (**I**). In other words, they assumed that in the dithionated product, (i) each thiosulfonic group was *ortho*- to an amino group and (ii) the two thiosulfonic acid groups were *para*- to each other and hence believed that the resulting cyclised products were the aforesaid linear benzobisthiazoles, **IIa** and **IIb** (Type I). The reactions are depicted in **Scheme 12**.

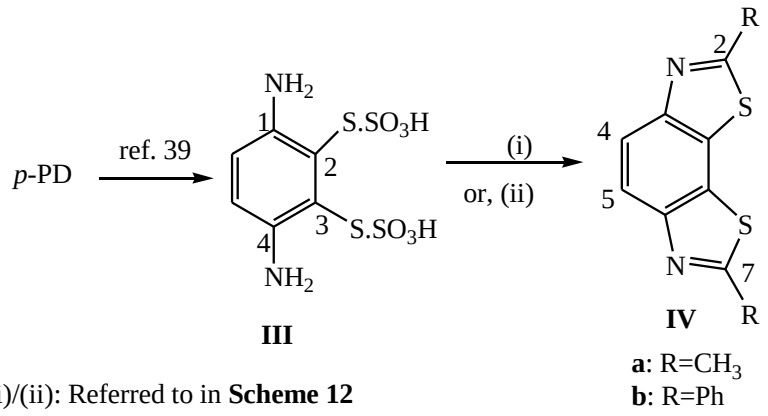


(i): Ac_2O/c. H_2SO_4, heat, few min
(ii): PhCHO/AcOH, 230-240°C, 0.5 h

Scheme 12

In the late sixties, three independent groups[40-42] synthesised 2,6-dimethyl, 2,6-diamino- and 2,6-dimethylaminobenzo[1,2-*d*:4,5-*d'*]bisthiazoles following established literature procedures. They also repeated Green and Perkin's work. From a consideration of the UV, IR and NMR spectra as well as the dipole moments of both sets of benzobisthiazoles, they demonstrated that the compounds prepared by Green and Perkin were actually the angular products, i.e. 2,7-disubstituted benzo[1,2-*d*:4,3-*d'*] bisthiazoles (Type IV).

It thus became evident from the aforesaid studies that the presumed 1,2,4,5-configuration of the intermediate diaminobenzene dithiosulfonic acid (**I**) was wrong. This product had indeed the 1,2,3,4-tetrasubstituted benzene structure (**III**), and the resulting products were naturally the angular isomers (**IVa**,**b**). The actual work undertaken by Green and Perkin is represented in **Scheme 13**.



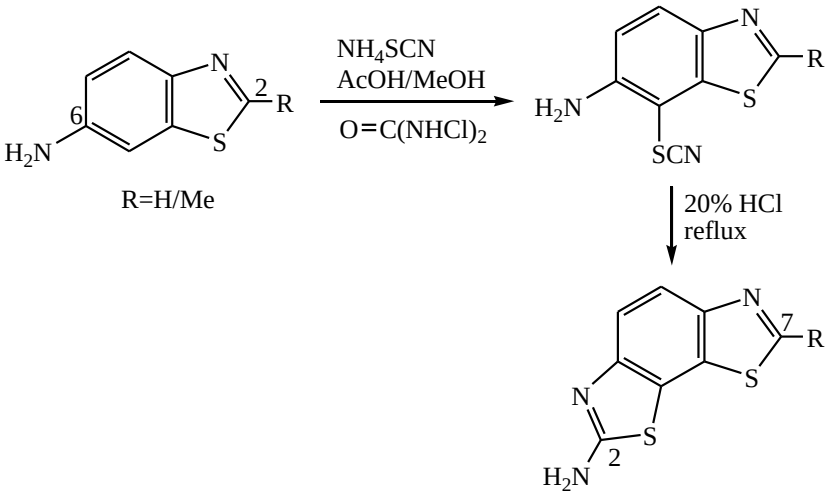
(i)/(ii): Referred to in **Scheme 12**

Scheme 13

It requires to be brought to the fore that, subsequently to Green and Perkin's work,[39] some reports[58,59] came out where the authors prepared benzobisthiazoles starting from diaminobenzene dithiosulfonic acid, following the report of Green and Perkin.[39] Now that the structure of the disulfonic acid was revised, the benzobisthiazoles prepared by these workers did not have the linear structures (Type I) claimed by them; these were actually the angular benzobisthiazoles (Type IV).

2.4.2 Staring from 6-Aminobenzothiazole[60]

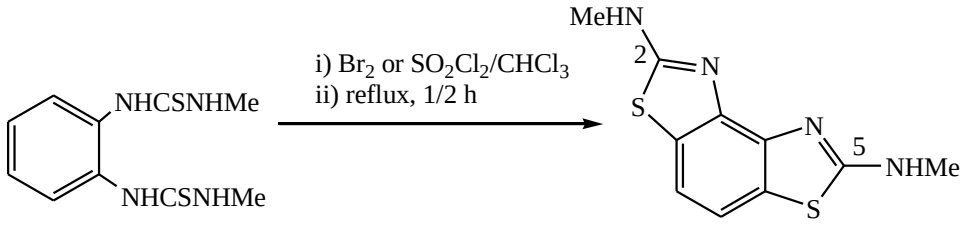
Two benzobisthiazoles of Type IV were prepared from 6-amino and 2-methyl-6-aminobenzothiazoles by thiocyanation (using ammonium thiocyanate, acetic acid and dichlorourea), followed by acid-catalysed cyclisation (**Scheme 14**).[60]



Scheme 14

2.5 Preparation of Benzo[1,2-d:6,5-d′]bisthiazoles (Type V)[40]

A member of this class of benzobisthiazoles was prepared by the cyclisation of *ortho*-phenylenebis(*N*′-methylthiourea) by cyclisation with bromine or sulphuryl chloride in chloroform (**Scheme 15**).



o-phenylenebis(*N*'-methylthiourea) 2,5-Dimethylaminobenzo[1,2-*d*:6,5-*d*']bisthiazole

Scheme 15

Moreover, other members of Type V were also prepared by derivatisation of members of this class.[43]

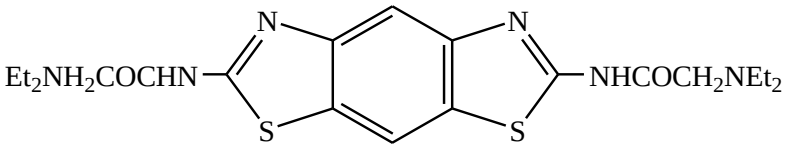
Following the above literature in 2010 Chakrabarty et al.[61] have reported a regioselective synthesis of various 2-substituted benzobisthiazoles by more or less a unified approach starting from 6-amino-benzothiazole. The amine was converted to: (i) 2-aminobenzobisthiazole by direct cyclisation (ii) 2-alkylamino/anilinobenzobisthiazoles *via* the corresponding 6-(*N'*-alkyl/phenyl)thioureidobenzothiazoles (iii) 2-alkylthio-benzobisthiazoles *via* the intermediacy of alkyl (benzothiazol-6-yl)dithiocarbamates and (iv) 2-alkylbenzobisthiazoles from the *N*-(6-benzothiazolyl) thioamides.

In the same year Mike et al.[62] have reported the synthesis of several synthetically useful 2,6-disubstituted benzobisthiazoles using Lewis acid as catalyst. It was a ring-closing reaction between substituted orthoesters and diamino benzene dithiol. The resulting benzobisthiazoles were obtained in good yields.

3. BIOLOGICAL ACTIVITY

A few references revealed that the benzobisthiazoles derivatives demonstrate potent anti-inflammatory, antibacterial, antifungal and antiprotozoal activity.[59,43,63] In general, linear benzobisthiazoles have been found to display higher biological activity than their angular counterparts.[59,43]

In 1992, Cullen et al.[43] have reported that 2,6-bis(*N*,*N*-diethylamino) benzo [1,2-*d*:5,4-*d*'] bisthiazole was found to inhibit the swelling of the uninjected paw in the prophylactic adjuvant arthritis model with an ED_{50} of 2.3 mg/kg orally.



2,6-bis(N,N-diethylamino)benzo[1,2-*d*:5,4-*d*']bisthiazole

Few years later Chakrabarty et al.[61] have investigated the anti-inflammatory potential of benzobisthiazole derivatives by measuring their ability to inhibit cyclooxygenase (COX). The

benzobisthiazoles were screened for inhibiton of both COX-1 and COX-2 using naproxen[64] as the standard following a recent protocol.[65,66] In the benzobisthiazole series, the methylamino derivative was most active, the anilino and the methylthio derivatives were less active and the rest displayed poor activity. 2-Methylthiobenzobisthiazole exhibited the best COX-2 inhibition (36%), followed by the 2-amino derivative. Although the 2-substituted benzobisthiazoles possessed the lowest COX-1 inhibitory activity, they displayed better COX-2 inhibition. All the synthesised compounds are less potent COX-1 and COX-2 inhibitors than naproxen.

In 2013 in another report[67], angular benzobisthiazole derivatives with a benzamide substitution (phenyl ring bearing different substitution) were recognized as novel helicase inhibitors through high throughput screening against purified Staphylococcus aureus and Bacillus anthracis replicative helicases. Initial investigation of structure-activity relationships (SARs) focused on the benzamide portion of the benzobisthiazole scaffold.

In 2016, again angular benzobisthiazole moiety was identified as selective and potent inhibitor for CLK protein kinase family members by Prak et al. [68]

4. MISCELLANEOUS APPLICATIONS

- In 2015, it was reported that organic benzobisthiazolium [69] salts bring various advantages in the field of Non Linear Optical materials, due to their improved solubility, greater stability (including photostability) and mainly enhanced Intramolecular Charge Transfer.
- In 2009 Ahmed et al.[70] recognized that the incorporation of benzobisthiazole into a regioregular poly(3-alkylthiophene) improve the oxidative stability by increasing the ionization potential (IP), thermal stability, inter chain interactions and thus enhance the charge transport properties of the polymers. The new copolymer semiconductor indeed showed an increased ionization potential and robust thermal and air stability.
- Polybenzobisthiazole were used in electronic applications as electron transport materials[71] in organic light-emitting diodes,[72] as nonlinear optical materials,[73-75] and as charge photogeneration materials in xerographic photoreceptors.[76-78] Light-emitting diodes containing polybenzobisthiazole electron transport layer were found to be stable in air for over a period of 10 months.[71]
- Materials based on benzobisthiazole units also showed other attractive electronic properties, such as high fluorescence, thermal stability, high electron affinity, electroluminescence properties,[79,80] and nonlinear optical properties. [72,81–89] As a result of these properties, such

materials have been used as electron transport materials in OLEDs[72], charge photogeneration materials[90,77] field-effect transistors and solar cells.[91-93]

5. CONCLUSION

This review article provides an extensive overview for the synthesis of various substituted benzobisthiazoles. Few biological applications of benzobisthiazoles and its derivatives were also brought to vanguard. Besides different uses of benzobisthiazole moiety as well as their polymers was discussed in brief. The current review is significant and holds the promise of being useful in the study of benzobisthiazoles.

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