BIS (BENZOTRIAZOL-1-YL) METHANETHIONE: NON-TOXIC VERSATILE THIOPHOSGENE EQUIVALENT

Archana Singh, Raju R. Kale, Bhuwan B. Mishra, V. Tripathi, and Vinod K. Tiwari*

Introduction

Benzotriazole methodology offers a well known versatile synthetic tool in organic synthesis and has gained extensive popularity since past few decades.[1-2] Nowadays benzoriazole mediated methodology magnificently used in construction of diverse range of biologically active molecules and heterocyclic skeleton. Benzotriazole easily introduce into a chemical moiety by a vast variety of reaction and easily removed at the end of reaction sequence without affecting the other functional group. It significantly influence the activity of other parts of molecule better in comparison to many other groups like phenyl, vinyl etc.

Activation of benzotriazole with other groups

The synthesis of furthermore functionalized benzotriazole is considered to become important subject for synthetic and biological researches since they are expected to exhibit novel properties applicable to such fields. Comparison of benzotriazole activation with other groups is shown below in **Figure 1.**

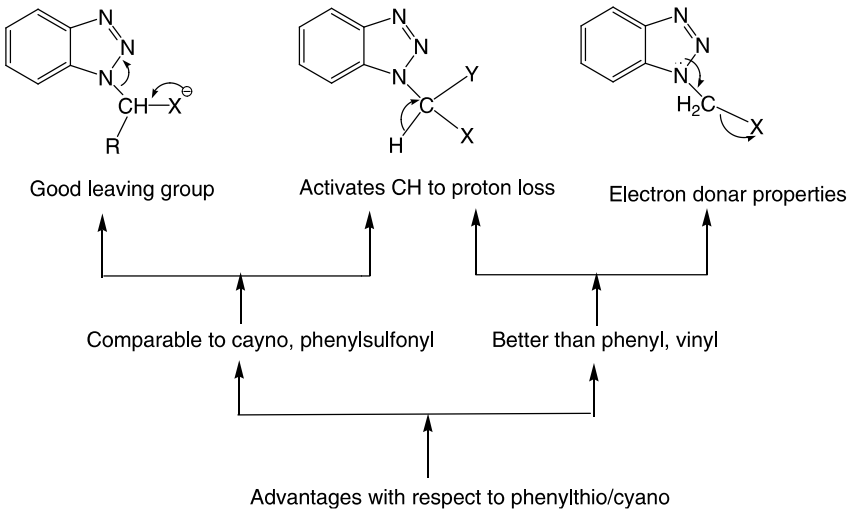


Figure - 1 Activation through benzotriazole

In comparison to many other substituents including halogen, benzotriazole is well known to acts as a leaving group as well as the stability of benzotriazole intermediate/synthons makes it more attractive synthons for organic chemist. Compounds with a benzotriazolyl group R to an amino or ether functionality (X, NR_2, OR) are stable, nonvolatile, easily prepared, and versatile, while their halogen analogues are physiologically dangerous and often too reactive to be conveniently used as reagents.[3-9]

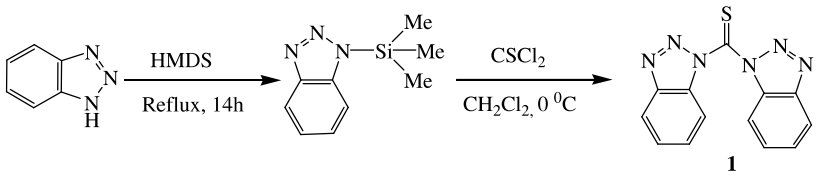
*Department of Chemistry, Faculty of Science, Banaras Hindu University, Varanasi, UP-221005, India.

Benzotriazole based synthetic auxiliary also offers many advantages particularly being inexpensive, non-toxic, and have sufficient stability.[2] Very recently with the help of TGA, DTA , DSC analyses confirm that benzotriazole is significantly more stable than 1,2,3-triazole.[10] These properties make *N*-substituted derivatives of benzotriazole sufficiently stable as synthetic auxiliary possess both electron donating and electron withdrawing properties and due to this it show very interesting reaction with the compounds containing heteroatoms especially O, N and S. In past few decades, benzotriazole draws enormous attention and explored in organic synthesis as a new synthetic methodology, catalyst in several reactions such as Baylis Hillman[11] and various coupling reactions and recently as light-activatable DNA cleaving agents.[12]

All these advantage and inertness with stability of benzotriazole ring system always attracts increasing interest of synthetic chemist for the implementation of new methods on this moiety to provide new horizon to synthetic chemistry by preparing many more new Bt mediated synthons which can replace old, conventional and multistep preparative method by new, convenient and simple methodology for the synthesis of useful drugs, biologically active compounds, and many natural product analogues.

Bis **(benzotriazol-1-yl) methanethione**

Bis(benzotriazol-1-yl)methanethione was obtained as yellow crystal (m.p. 170-171 ^{0}C) starting from benzotriazole in high yield (**Scheme 1**).[13] It can also be obtained directly from benzotriazole reacting with thiophosgene.



Scheme - 1

Synthetic applications of bis-(benzotrizol-1-yl) methanethione

Bis(benzotriazolyl) methanethione is a reagent derived from benzotriazole, now proved itself a very effective thiophosgene equivalent in thioacylation[14] and in synthesis of different chemically and biologically active compounds. Compared to thiophosgene,[15] bis-(benzotriazolyl) methanethione is found to more advantageous not because of its less toxicity but also due to its high stability that can be stored for years at room temperature and crystalline solid nature which make it easy to handle during the course of reaction (**Figure 2**).

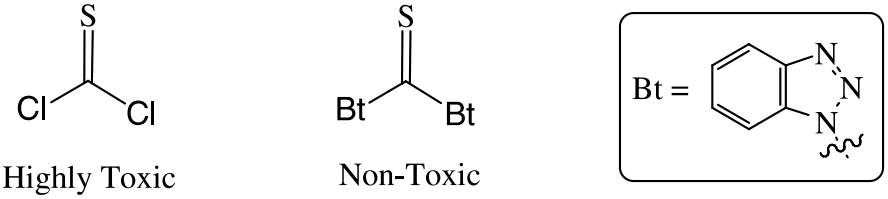


Figure - 2 Structure of Bis(benzotriazolyl)methanethione

It also acts as a precursor in synthetic chemistry for the preparation of many useful reagents, which take part in the synthesis of a vast range of valuable organic molecules like trisubstitued guanidines, N-hydroxy, N-amino guanidines, *â*-enamino thioic acid derivatives, thiosemicarbazide and N- hydroxythiourea. Some representative reactions and reagents derived from *bis*(benzotriazol-1-yl) methanethione are presentated in **Figure 3**.

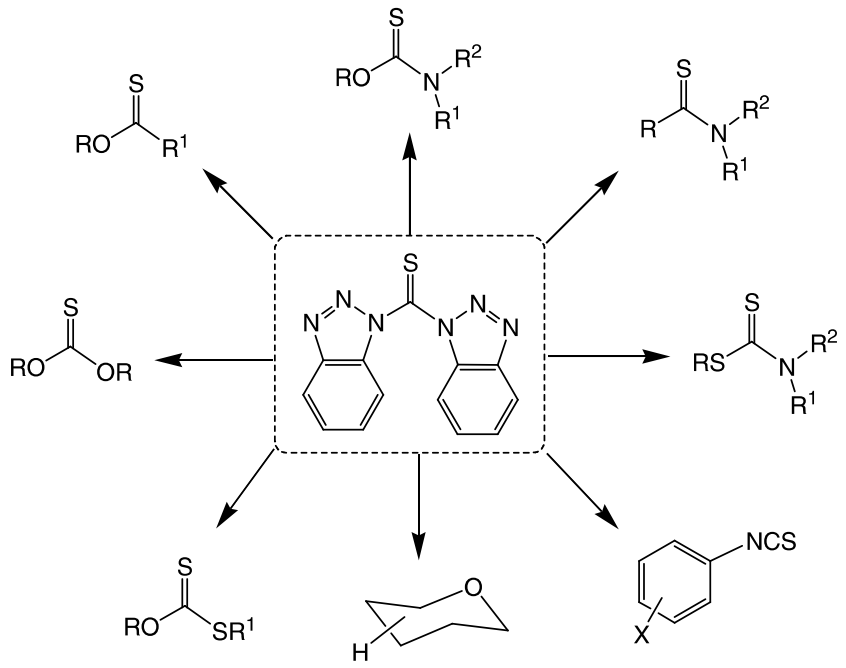
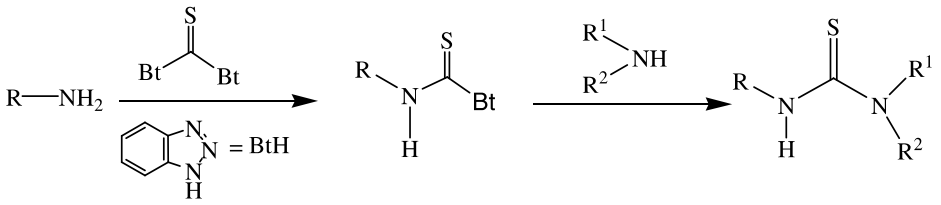


Figure - 3 *Bis*-(benzotriazol-1-yl) methanethione mediated reagents

Preparation of symmetrical/unsymmetrical thioureas

Thioureas are important organic compounds of considerable use in medicinal chemistry due its biological activity as antibacterial, antimicrobial, fungicidal, herbicidal, rodenticidal etc.[16.] Thioureas are also most important synthetic building block for synthesis of five and six membered heterocycles.[17]

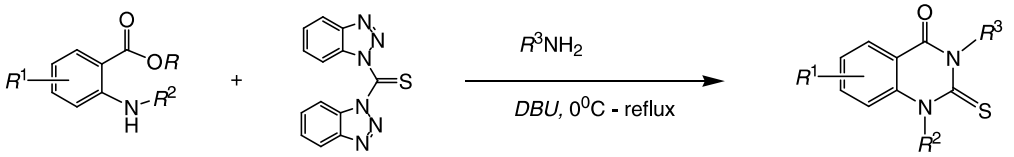
Bis (benzotrizol-1-yl) methanethione has been successfully utilized as isothiocynate equivalent for the efficient synthesis of secondary and tertiary thioureas in high to excellent yield (**Scheme 2**).[18]



Scheme - 2

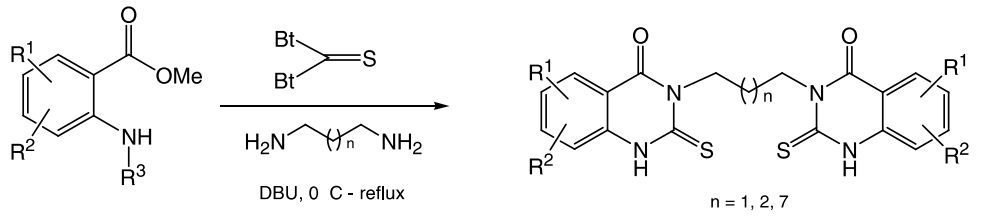
Synthesis of quinazolinone derivatives

Methaqualone (**Figure 3**), the most popular quinazolinone drug synthesized in 1951 for its antimalarial effect,[19] is currently being used for the assessment of the abuse liability of sedative hypnotic drugs.[20] In addition of associated with the diverse range of pharmacological activities, quinazolinone skeleton is frequently encountered as building block for hundreds of alkaloid.[21] The preparative methods leading to these molecules mainly include the reaction of substituted anthranilic acids or its functional derivatives with isothiocyanates, thioureas, excess of refluxing formamide, imidates, methyl N-aryldithiocarbamates, ammonium aryldithiocarbamates, amine and CS_2 in basic medium, RNHCOOEt and imidazole, amine and sodium cyanate, $CSCl_2$ either in presence of NEt_3 or hydrazine, polymer supported $FeCl_3$, orthoesters, and amines under solvent free conditions, anilines, CS_2,



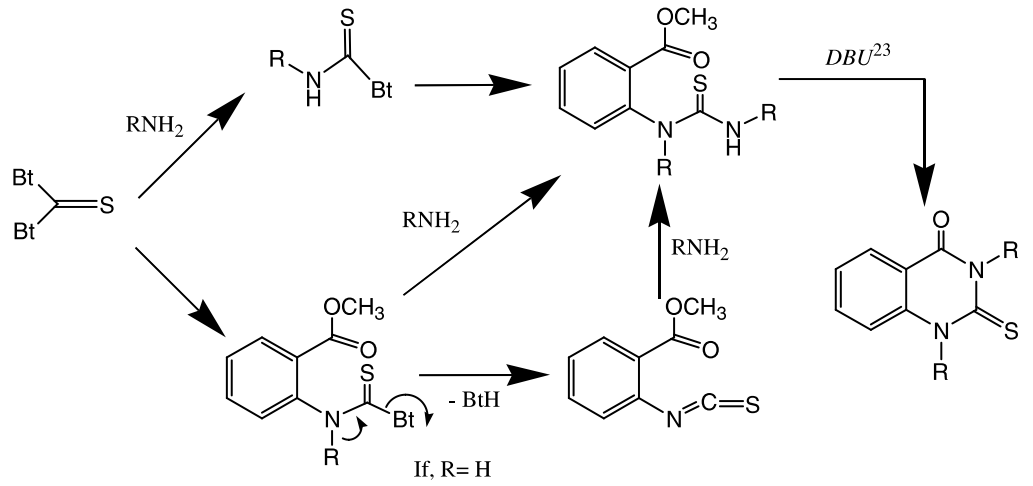
Scheme - 3

Similar reaction of methyl anthranilate with diamines and *bis*-(benzotriazol-1-yl)methanethione in presence of *DBU* using anhydrous dichloromethane as solvent afforded the desired quianzolinone derivative in good yield (**Scheme 4**).[23]



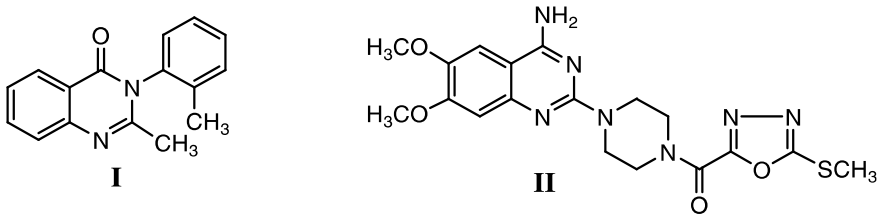
Scheme - 4

In our one-pot addition-cyclization, yields are high particularly with N^1-unsubstituted anthranilic esters; however with N^1-substituted one, e.g. NCH_3, the reaction yield was comparatively low, *i.e.* in general with N^1-unsubstituted derivatives, the cyclization was facile. The reason can easily be understood as depicted in **Scheme 5**. The mechanism proposed for the reaction involves the addition of amine to *bis*-(benzotriazol-1-yl)methanethione *via* two different route A and B resulting in the formation of thiocarbamoylbenzotriazoles (that on elimination of BtH, in case of N^1 -unsubstitution resulted in isothiocyanates) that on addition of anthranilic ester yielded uncyclized thiourea. Further cyclization proceeds in a similar reported way,[24] which involves abstraction of a proton from the terminal amido functionality by *DBU* giving a thioureidyl anion that results in thioquinazolinones through cyclative amidation.



Scheme - 5

Because of interesting metabolic profile and ability to engage in hydrogen bonding, [1,3,4]-oxadiazoles and thiadiazole are attractive pharmacophores that commonly utilized as scaffold in medicinal chemistry. 2-Amino- [1,3,4]-oxadiazoles itself have demonstrated broad spectrum of biological activity including muscle relaxants and antiomitotics. Tiodazosin, a hybrid of quinazoline and [1,3,4]-oxadiazole heterocycles has been marketed as antihypertensive agents (Figure 4).[25] Compound having thiazole ring also possessing a wide spectrum of biological activity.



I **II**

Figure - 4 Structure of Methaqualone (**I**) and Tiodazosin (**II**)

In recent years microwave assisted chemistry has become an emerging tool for the synthesis of diverse range of molecules for medicinal interest over the conventional method. In this relevance, we turned our attention to *bis*-(benzotriazolyl)-methanethione and amidine base *DABCO*, and developed a simple and direct one-pot procedure that was compatible with other heterocyclic ring and substituents. Thus, *MW* irradiation of methyl anthranilate, *bis*-(benzotriazol-1-yl)methanethione, and 5-Phenyl-[1,3,4] thiadiazol-2-yl-amine in presence of *DABCO* as catalyst afforded the compound in good yield, but that could not be isolated free from *DABCO* after elution with 20% EtOAc:*n*-hexane through silica gel column (**Figure 5**).

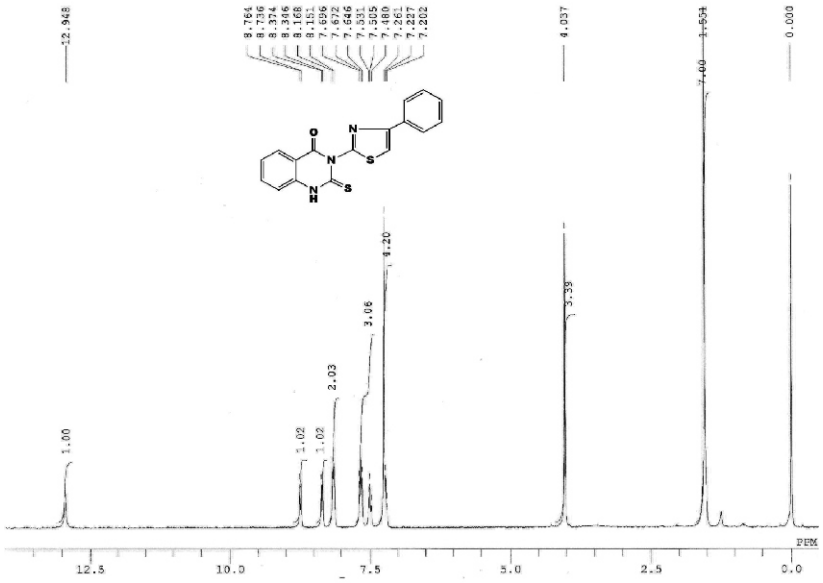
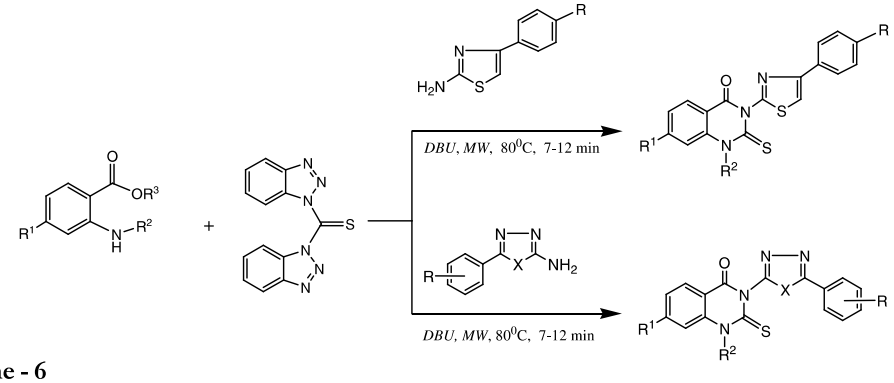


Figure - 5 ^{1}H NMR of synthesized quinazolinone (*DABCO* catalyzed reaction)

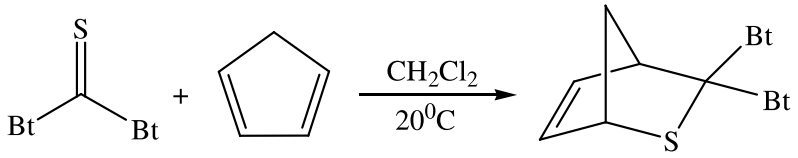
We reported a microwave-assisted simple, convenient, and high yielding synthetic methodology for the diverse thioquinozolinone by the amidine base catalyzed one-pot reaction of anthranilate ester, *bis*-(benzotriazolyl)-methanethione, and heterocyclic amines containing thiazole, [1,3,4]-oxadiazoles and [1,3,4]- thiadiazole heterocycles (**Scheme 6**). [26]



Scheme - 6

Diels-Alder Addition of bis(benzotriazole-1-yl)methanethione

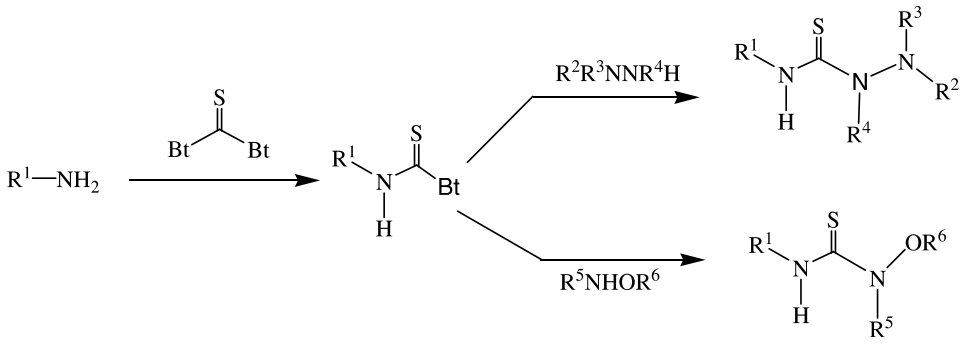
Diels-Alder Addition of bis(benzotriazole-1-yl)methanethione to cyclopentadiene provides the moisture-stable crystalline adduct in excellent yield, which can be store at room temperature for several months without any deterioration like its thiophasgene analogue which are unstable and decompose to black tar if not kept at dry ice temperature.[27] This crystalline adduct is a very useful precursor for the synthesis of *cis*-3, 5-fused mercapto esters.



Scheme - 7

Synthesis of Thiosemicarbazides and *N*-hydroxythioureas

Thiosemicarbazides possess a wide range of interesting and important biochemical and pharmaceutical properties. Thiosemicarbazides act as a building block for the synthesis of diverse range of heterocycles possessing a broad spectrum of biological activities.[28] *S*-methyl-*N*-hydroxyisothiourea is known to inhibit nitrous oxide syntheses (NOS).[29] By using bis(benzotriazole-1-yl)methanethione as a precursor with reaction of the appropriate hydrazine and corresponding hydroxylamine, we can also synthesized Thiosemicarbazides and *N*-hydroxythioureas of diverse substitution patterns in excellent yields respectively **(Scheme 8)**.[30]

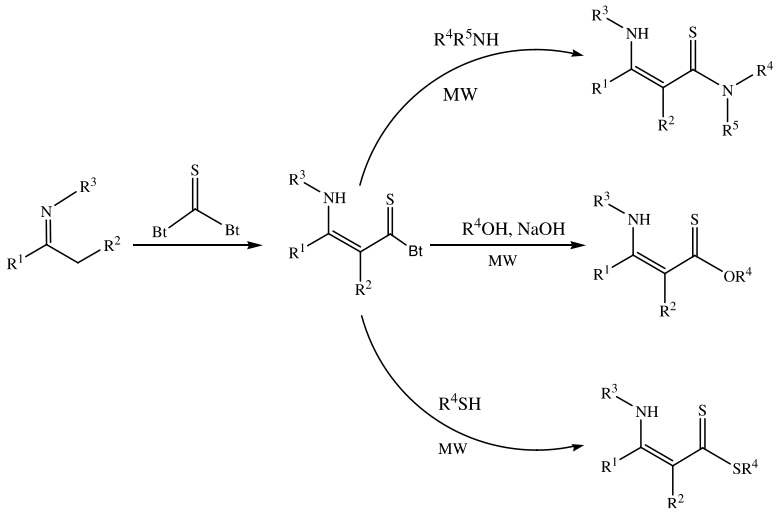


Scheme - 8

Synthesis of *â*-enamino thioic acid derivatives

â-Enaminothioic acids are important synthetic building block for the synthesis of diverse heterocycles like pyrazole, 4-aminoquinolines, dihydrothiopyrans, thiazoline, thiazolin-4-one, 1,3-thiazolin-4-one, 6H-1,3-thiazines, *â*-keto thioic acid derivatives, as well as useful precursors for liquid crystals.[31-33]

Reaction of bis(benzotriazole-1-yl)methanethione **(1)** with imines gives air stable benzotriazolyl *â*-enaminothione and this benzotriazolyl â-enaminothione which proved their utilization as a very useful reagent for simple and efficient preparation of â-enamino thioic acid derivatives (thioamides, thioesters and dithioesters) in considerable yields *via* microwave mediated nucleophilic substitution of the benzotriazolyl moiety. Reaction of benzotriazolyl *â*-enaminothione with secondary amines gave *â*-enamino thioamide, with alcohols or thiols in the presence of sodium or potassium hydroxide give thioesters and dithioesters, respectively (**Scheme 9**).[34]

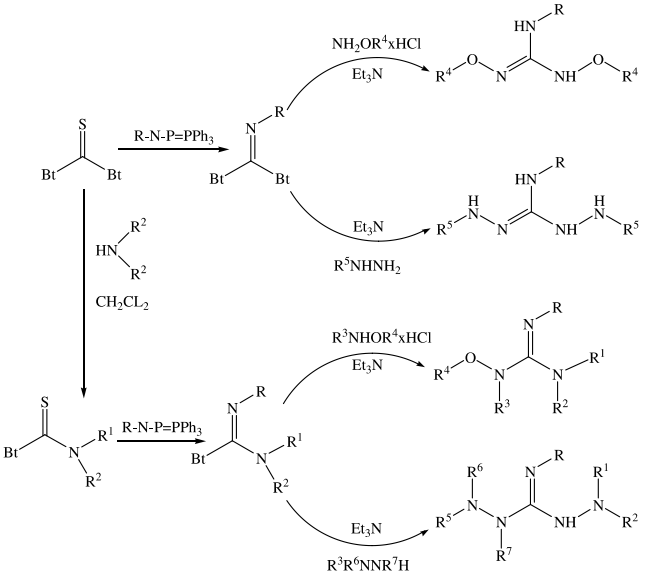


Scheme - 9

Synthesis of di-*N*-hydroxy and *N*-aminoguanidines

Guanidines are not only synthetically important unit combines *p*-donor and *p*-acceptor nitrogens but also biologically important structural units which show anti-tumor properties in Guanidino-containing drugs such as MIBG and MGBG.[35] So guanidine containing drug's provide a new hope for the treatment of many metabolic diseases, cancer, cardiovascular diseases, and diabetes.[36]

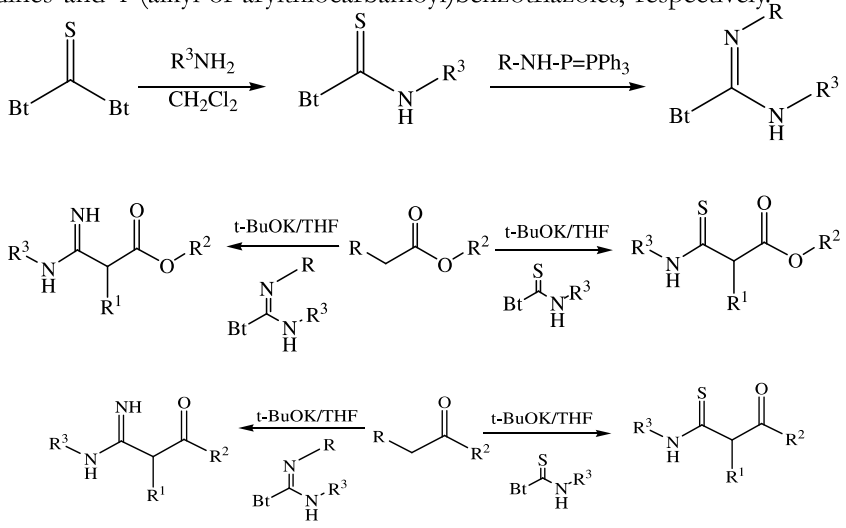
Reagents of classes (bis-benzotriazol-1-yl-methylene)amines**,** benzotriazole-1-carboxamidines and benzotriazole-1-carboximidamides that can readily react with diverse hydroxylamine and hydrazine giving mono, symmetrical di-*N*-hydroxy- and *N*-aminoguanidines with different substitution patterns in good yields can be synthesized by using bis(benzotriazole-1-yl)methanethione.[37]



Scheme - 10

C-Aminoimidoylated and *C*-thiocarbamoylated

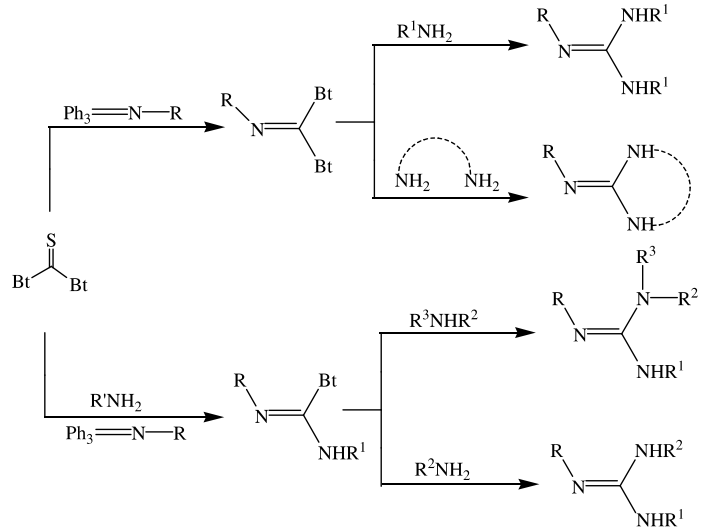
Esters, sulfones, and ketones were *C*-aminoimidoylated and *C*-thiocarbamoylated with the class of reagents obtained from bis(benzotriazole-1-yl)methanethione, benzotriazole-1-carboxamidines and 1-(alkyl-or-arylthiocarbamoyl)benzotriazoles, respectively.[38]



Scheme 11

Synthesis of 1, 2, 3, trisubstituted guanidine

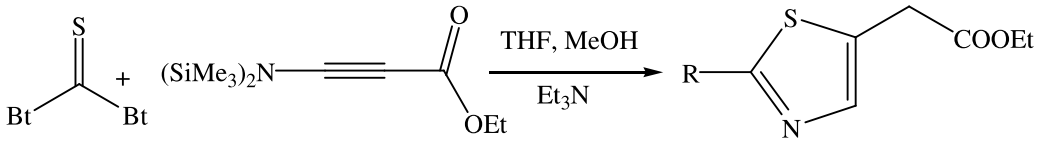
Several pharmacologically significant natural products containing guanidine skeleton have been isolated from plants and other microorganisms.[39] Katritzky *et al* reported a high yielding synthesis of acyclic and cyclic 1,2,3, trisubstituted guanidine with a different method for the guanylation of various primary and secondary amines by the use of new class of reagents (bis-benzotriazol-1-yl-methylene)amines and benzotriazole-1-carboxamidines and these reagents are prepared by bis(benzotriazole-1-yl)methanethione (**Scheme 12**).[40]



Scheme 12

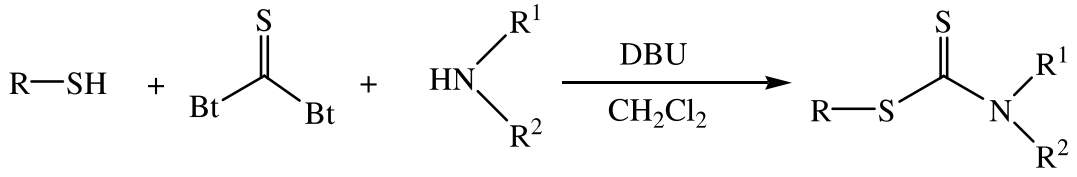
Synthesis of thiazole derivatives

Thiazole nucleus not only plays a very important role in metabolism, but also known for a diverse range of pharmacological effects. Sasmal et al have demonstrated a bis(benzotriazole-1-yl)methanethione mediated one-pot efficient methodology for the synthesis of thiozol ring *via* N-desilylation, thioacylation followed by cycloisomerisation in an intramolecular thia-Michael fashion (**Scheme 13**).[41]



Scheme 13

Bt-mediated synthesis of Dithiocarbamates: Organic dithiocarbamates (*DTC*s) have received much attention by synthetic and medicinal chemists due to their interesting chemistry and diverse pharmacological properties. The *DTC* framework is ubiquitously found in a variety of biologically active molecules and it gained importance as building blocks, combinatorial scaffold, as well as intermediates in organic synthesis to develop new active chemical entities (NCE's). [42] In spite of the growing interest in applications of these compounds, preparative methods available for their synthesis are still limited. Most of the synthetic methods are associated with one or the other limitations including low availability of starting material, employment of harsh reaction conditions, high reaction temperatures, long reaction times, low yields, and more over required two or more steps. Recently we have developed a convenient and high yielding method for the synthesis of diverse dithiocarbamates having various substituents including alkyl, aryl, heteroaryl, and alkylaryl at the thiol chain or at the amine chain or at both thiol and amine chains by the one-pot reaction of mercaptans, amines, and *bis*-(benzotriazolyl)-methanethione in presence of amidine base under mild reaction conditions (Scheme **14**).[43]



Scheme 14

The above described methodology has been successfully applied for the synthesis of N/S glycosyl dithiocarbamates.[44] Structures of some representative glycosyl dithiocarbamates synthesized by our reported one-pot benzotriazole mediated methodology are given below:

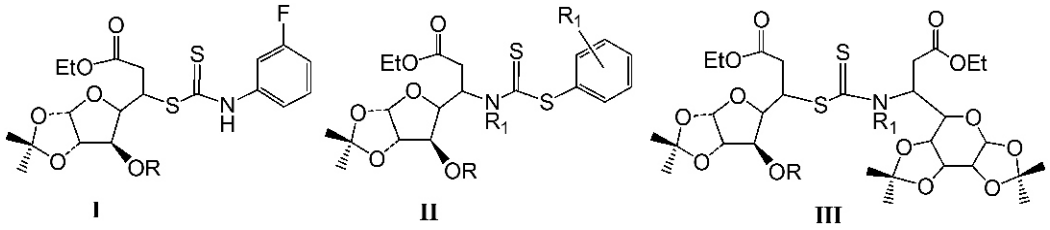
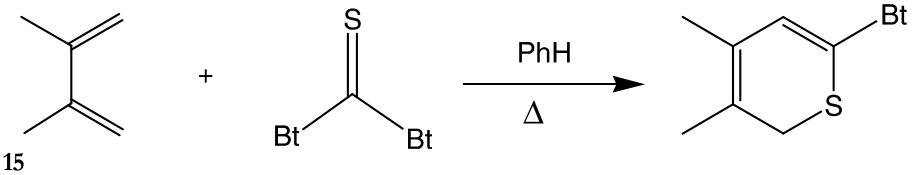


Figure - 6 Some representative glycosyl DTC

Bis(benzotriazole-1-yl)methanethione mediated cycloaddition

It is found that thiocarbonyl transfer reagents undergo ready cycloaddition with a variety of systems gives stable crystalline solid rather then unstable adduct formed by its parent thiophosgene.[45] Bis(benzotriazole-1-yl)methanethione on reaction with 2, 3 dimethyl-1, 3,-butadiene gave 3,4-dimethyl-6-(benzotriazol-1-yl)-2H-thiapyran.[46]



Scheme 15

Conclusion

Present review is focused on preparation and vast synthetic applications of bis(benzotriazole-1-yl)methanethione, that has been shown advantageous over thiophosgene as being more effective equivalent in numerous important chemical reactions and more over due to non-toxic nature of benzotriazole containing molecules. It plays significant role in several chemical reactions particularly for the synthesis of thiourea, *N*- hydroxythiourea, thiosemicarbazide, triazoles, thiozoles, guanidines, *N*-hydroxy-*N*-amino guanidines, *â*-enamino thioic acids, diverse dithiocarbamates, and quinazolinones etc. This synthetic auxiliary may serve as a synthetic key, structural, and functional tool for future synthetic organic chemistry.

Acknowledgements

We thank Department of Science and Technology (DST), New Delhi for financial assistance (DST Fast Track Project No M-48-73).

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