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1,2,4,5-Tetrazines as platform molecules for energetic materials and pharmaceuticals

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Abstract: This short review provides various routes for the synthesis of *sym*-tetrazines and their potential applications mainly as energetic compounds and pharmaceuticals. *Sym*-tetrazines can be synthesized from variable chemical sources such as nitriles, imidates, amidines, thioamidines and substituted hydrazines. Moreover, these molecules have high positive enthalpies of formation and the nitrogen rich ring system is redox active capable of reversibly forming a stable radical anion, therefore promoting their use in the preparation of energetic materials and fluorescent compounds.

Keywords: 1,2,4,5-Tetrazines, Antitumor, anticancer and antimicrobial agents, Monopropellants, Energy storage compounds.

Introduction

Tetrazine is benzene like molecule in which the four CH units are replaced by four electronegative nitrogen atoms. Out of the three possible isomers, 1,2,3,5-tetrazine, 1,2,3,4-tetrazine and 1,2,4,5-tetrazine later two are of immense importance and have been studied synthetically [1]. Among these derivatives, 1,2,4,5-tetrazine is symmetrical and also known as *sym*-tetrazine or *s*-tetrazine. It represents an important class of heterocyclic compounds that further provides access to wide range of heterocycles and natural products via rearrangement or by chemical reactions. 1,2,4,5-Tetrazines also posses antitumor activity [2] and have been used as pesticides and herbicides [3], and in the synthesis of high energy materials [4] because of the high reduction potentials due to the presence of four nitrogen atoms [5]. They can be reversibly transformed into a stable anion-radical and this property has been employed for studying their fluorescence behavior [6]. The most common method for the preparation of tetrazine nucleus is the reaction of nitrile with hydrazine (Scheme **1**).

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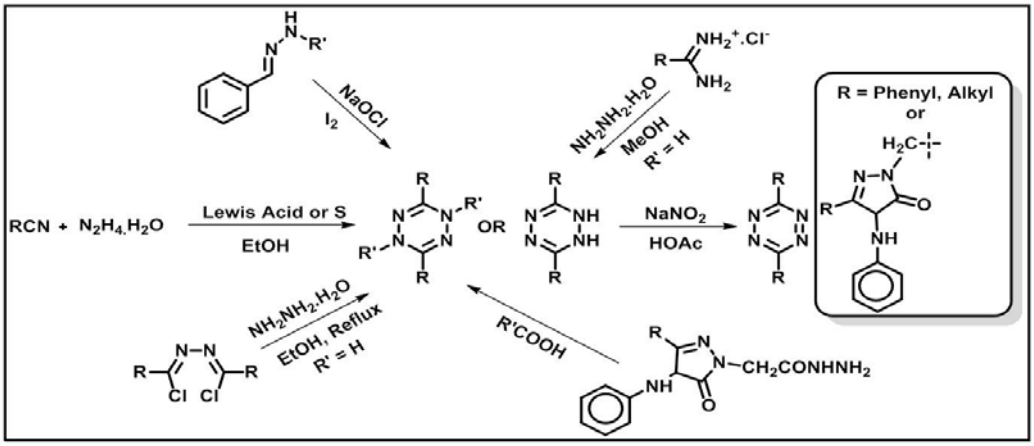
But this reaction leads to very low yield of the tetrazine product, which is 1,2-dihydro-1,2,4,5-tetrazine derivative. In order to increase the yield a catalyst is generally required. Sulfur is the most commonly used catalyst [7] in this case and provides enhanced yields of 1,2-dihydro-1,2,4,5-tetrazines. In order to convert this 1,2-dihydro-1,2,4,5-tetrazine into 1,2,4,5-tetrazine, oxidation process is generally required. The oxidation step can either be performed after the separation of 1,2-dihydro-1,2,4,5-tetrazine product or under "*in situ*" conditions without the isolation of the product. Modification of this method has been applied by various researchers for the synthesis of 1,2,4,5-tetrazine derivatives using multiple precursors. Recently, Devraj et. al [8] have used Lewis acidic metal salts for the synthesis of tetrazines directly from nitriles and hydrazine, without involving the isolation of 1,2-dihydro-1,2,4,5-tetrazines. The method provides high yields of tetrazine product and involves oxidation step performed by $NaNO_2$ in presence of HCl. Substituted hydrazine derivatives can also be employed for the synthesis of 1,2,4,5-tetrazine derivatives. In a typical example 1-benzylidine-2-alkylhydrazines were used to synthesize 1,2,4,5-tetrazine derivatives [9] by I_2 and NaOCl. Hydrazine

substituted with 4-amino-1,2,4-triazole derivative was also used for the generation of 1,2,4,5-tetrazole nucleus by smile rearrangement. Triazole[4,3-b][1,2,4,5] tetrazine has been prepared by the reaction of 4-amino-5-methyl-1,2,4-triazole-3-thiol with hydrozonoyl halides using chitosan as a basic catalyst under microwave irradiation [10]. Nucleophilic attack of hydrazine or hydrazine hydrate on imidates, amidines and thioamidines [11] is also used for their synthesis.

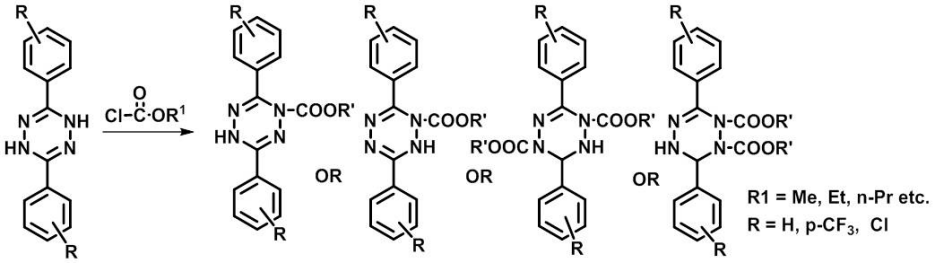


Scheme 1: Different Synthetic Routes for the synthesis of 1,2,4,5-tetrazines.

Results and discussion

Chemical Conversions and Biological Activity

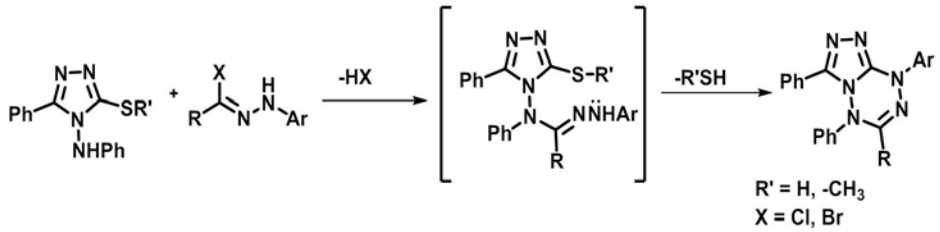
The nucleophilic nature of nitrogen in the 1,2-dihydro-1,2,4,5-tetrazine nucleus is helpful for the preparation of different derivatives by substitution reaction. *s*-Tetrazine undergo S_NAr reaction in presence of strong base such as NaH or $NaOCH_3$, and the reaction of dimethylthio-*s*-tetrazine was used for the preparation of $–OCH_3$ substituted derivatives from a strong base $NaOCH_3$ [12]. The inverse demand Diels-Alder cycloaddition reaction [13] was used for their further derivatization. Rao et al [14] have performed nucleophilic substitution on chloroformates to synthesize different derivatives of *s*-tetrazine and (Scheme **2**) the compounds were found to have potential antitumor activity.



Scheme 2:Substitution of *s*-tetrazines with chloroformates to generate library of antitumor compounds.

Antimicrobial activity of 1,2,4-triazole[4,3-b][1,2,4,5]-tetrazines was evaluated by Altalbway et al.,[15] and they have synthesized these derivatives via the reaction of hydrozonoyl halides with 4-aminophenyl-5-phenyl-4H-1,2,4-triazoles (3-thio and its 3-methylthio derivatives) (Scheme **3**). Antitumor activity of different 3,6-bis(substitutedphenyl)-1,4-bis(substituted-phenylsulphonyl)-1,4-dihydro-1,2,4,5-tetrazines was evaluated by Hu et al [16], which were prepared *via* reaction of N-arylsulphonyl-chlorosubstituted phenyl hydrazine with trimethyl amine. Among the different compounds synthesized, 3,6-bis(6-methyl-pyridine-2-yl)-[1,2,4,5]tetrazine and the compound with 4-chloro-2-methyl-phenol

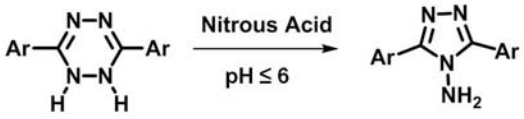
substituent exhibited potent anticancer activity. Antitumor potentials of these synthesized compounds were varied by changing the substituents at different positions.



Scheme 3: Synthesis of antimicrobial tetrazines from hydrozonoyl halides and 4-aminophenyl-3-(alkylthio)-5-phenyl-1,2,4-triazoles.

4-position in the tetrazine nucleus had strong effect on the antitumor activity of the compounds, bulky substituents at this position generally increases the antitumor potential to greater extent especially the carbonyl groups and amino group. 3- and 6- position also have important role to decide the anticancer potentials of these compounds, where the positively charged groups are beneficial for the antitumor effects. Larger groups at 3- and 6-position with hydrophobic segments generate less active compounds while substituents with methyl group increase the activity. Bulky groups at 1 and 4- positions played favorable role in the activity.

1,2-Dihydro-*s*-tetrazine can further be converted to 4-amino-1,2,4-triazoles under acidic conditions [17] (Scheme 4).

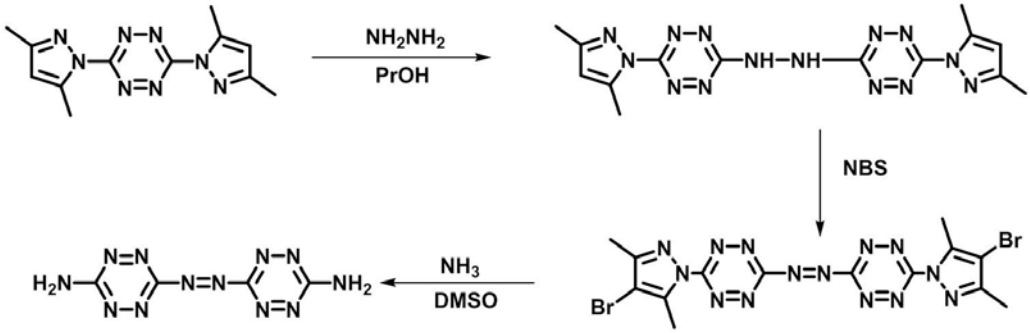


Scheme 4: Synthesis of biologically active triazoles from *s*-tetrazines under acidic conditions.

Product formation depends upon the acidic conditions used. Strong acidic conditions favour the formation of 4-amino-1,2,4-triazole product, whereas almost neutral or mild conditions favours generation of aromatic ring leading to 1,2,4,5-tetazines. Under highly acidic conditions (pH<2) formation of 1,3,4-oxadiazole product is favoured. This reaction has been used for the isomerization of different 1,2-dihydro-*s*-tetrazines into 4-amino-1,2,4-triazoles that have been demonstrated to posses interesting biological applications such as antifungal [18], anti-Inflammatory [19-20], antibacterial [21] and anticonvulsant activity [22].

Applications

Hydrazine is one of the most commonly used monopropellant compound [23] and its applications can be extended by trapping it into other derivatives such as in 1,2,4,5-tetrazines. Later not only have tailor-able properties but also possess high positive enthalpies of formation, high densities and good thermal stability. Nitrogen rich ring system in these molecules is redox active and capable of reversibly forming a stable radical anion. This promising property promotes their use for the synthesis of new energetic materials [24]. Tetrazine derivative 3,3´-azobis(6-amino-1,2,4,5-tetrazine) [25] exhibited high heat of formation (+ 862 $KJmole^{-1}$), and the compound was prepared from 3,6-bis(3,5-dimethyl-pyrazol-1-yl)-[1,2,4,5]tetrazine upon reaction with hydrazine in 2-propanol (Scheme 5). This compound was found to be thermally stable at 252^{o}C and was reported to have a drop weight impact value of 70 cm compared to 25 cm of the highly explosive HMX (octahydro-1,3,5,7-tetranitro-1,3,5,7-tetrazocine), thus highly energetic and explosive. Tetrazines are used in intracellular small molecule imaging [26], genetically targated protein tagging [27], post synthetic DNA labeling [28], nanoparticles based clinical dignostic [29], in vivo-imaging [30] and as bioorthogonal coupling agents [31-32]. In addition, they are used for the synthesis of different natural products [33], and also applied in material science [34] and coordination chemistry [35].



Scheme 5: Conversion of hydrazine into highly energetic *s*-tetrazine.

Conclusions

Irrespective of fact that 1,2,4,5-tetrazines have great biological potentials and ability for generating a new class of energetic compounds, they still have derived less attention in comparison to their isomeric 1,2,3,4-tetrazines. Potential risk (explosions) involved during their synthesis is one of the major hurdle in the preparation process. The ability of these molecules to act as potential antitumor agents and their unique behavior as a fluorescent compounds has derived considerable attention in recent years and is a good area for research. Simultaneously, better infrastructure such as specially designed hoods to prevent damage from explosions and prevention from the toxic chemicals (e.g. hydrazine and its derivatives) are also neccessary while working with these compounds.

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