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One-pot synthesis of oxazolidine-2-thione and thiozolidine-2-thione from sugar azido-alcohols

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ABSTRACT

A controlled and facile synthesis of various glycosyl 1,3-oxazolidine-2-thiones and 1,3- thiozolidine-2-thiones has been accomplished from corresponding sugar azido alcohols utilizing Staudinger reaction (PPh_3 and CS_2) *via* isothiocynate route. A series of reactions were performed to investigate the effects of CS_2 and PPh_3 on the selectivity of product formed. The excessive addition of CS_2 with PPh_3(1.2 equiv) afforded oxazolidine-2-thione alone, while the solitary addition of PPh_3 for 30 min followed by addition of CS_2 to the reaction mixture resulted both the products in different ratios, which were successfully isolated using column chromatography (SiO_2). Furthermore, synthesis of 1,3-oxathiolan-2-imine from glycosyl epoxide has also been attempted. Structures of all the developed compounds have been elucidated using extensive spectroscopic techniques including IR, NMR and MS analysis.

1. Introduction

In past decade, combinatorial chemistry has provided the path to achieve an assembly of privileged structures [1], particularly by incorporating heterocyclic scaffolds which found remarkable applications in medicinal chemistry as well as in chiral synthesis [2–4]. Numerous heterocyclic systems with two hetero atoms in the ring, such as, piperazine, morpholine, oxazole, thiazole etc. have been considered as biologically relevant scaffolds [5]. Similarly, five-membered heterocyclic ring systems like thiozolidine, thiozolidine-2-thione and oxazolidine-2-thiones have been identified as a vital scaffolds in medicinal chemistry and displayed a wide variety of biological activities such as D-fructose transporter inhibitors [6], antithyroid [7], antifertility [8], antibacterial [9], insecticidal [10], etc. Some representative biologically relevant thiozolidine-based molecules include antithyroid Epigoitrin **(I)** [11], dopamine β-hydroxylase inhibitor (**II**) [12], antifungal Fezatione (**III**) [13], herbicidal (**IV**) [14] and antiviral 2′,3′-thiocarbamate-based ribonucleoside (**V**) [15] (Fig. 1).

Carbohydrate moiety, due to its poly-functional nature, rigidity and chirality, possesses many unique stereo-chemical and functional aspects that are considered as essential features for the induction of selectivity and chiral discrimination in various chemical, metabolic and recognition processes [16–22]. Hence, functionality and structural variations are the key features due to which sugar molecules have appeared as the effective scaffolds for stereoselective synthesis and thus considered as nature's valuable gift to synthetic chemists [23]. A versatile synthetic intermediate 'isothiocyanate' has ability to undergo nucleophilic addition reactions and delivering a variety of interesting products of chemotherapeutic values [24]. Particularly, glycosyl isothiocyanates play crucial role in the synthesis of a wide spectrum of glycoconjugates and it has been found useful for the synthesis of glycosyl thiourea [25–27], although rarely used for the synthesis of 1,3-oxazolidine-2-thione. Incorporation of such scaffolds on carbohydrate moieties has been considered as an essential requirement in chemical biology [28,29], however development of a facile protocol is still challenging. Absence of direct precursors on natural sugars makes such creation difficult; yet their mechanical construction is not an easy task. Amino alcohols are found as suitable precursors for non carbohydrate derivatives, but use of azido alcohols for this purpose is limited [30]. Some common approaches for the synthesis of 1,3-oxazolidine-2-thiones is depicted in Scheme 1. The aziridine derivative, for example, 7-methyl-6-phenyl-7-azabicyclo[4,1,0]he[tan-2-ol, on refluxing with 1,1-thiocarbonyl diimidazole in

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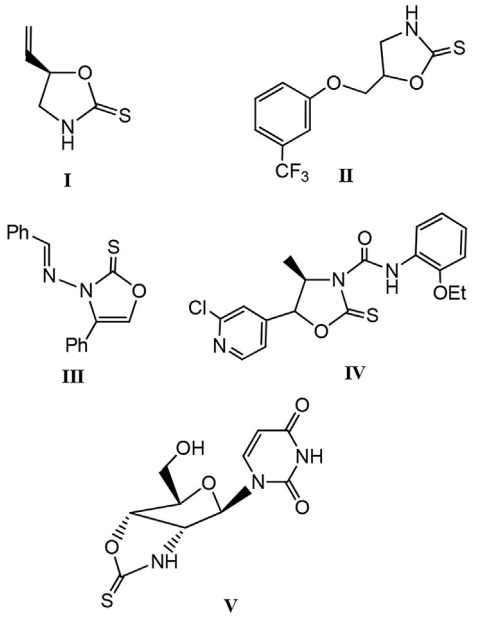
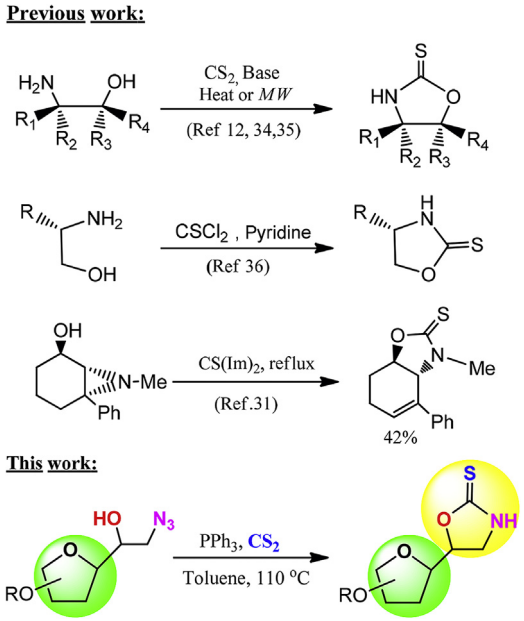


Fig. 1. Structure of some biologically relevant thiozolidine-based molecules.



Scheme 1. Common approaches for the synthesis of 1,3-oxazolidine-2-thiones.

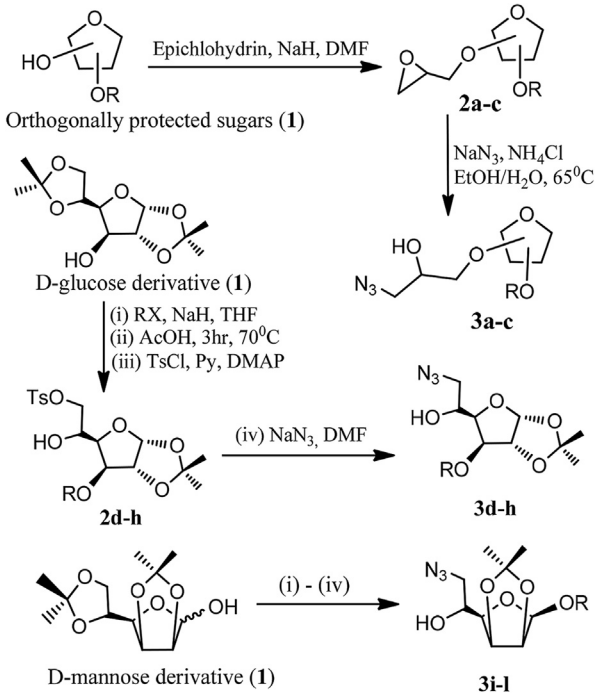
dichloromethane afforded the cyclic oxazolidine-2-thione alongwith the expected thiocarbonylimidazolide analog [31]. However, the method is little explored for an easy access of biologically relevant 1,3-oxazolidine-2-thiones [15,32,33]. In another way, amino alcohols, on treatment with CS_2, either under standard heating or under microwave (*MW*), have also been utilized to achieve good yields of respective oxazolidine-2-thiones [34,35]. Interestingly, related amino alcohols, on reacting with $CSCl_2$, afforded respective novel oxazolidine-2-thiones [36], however method has some serious limitations, notably the high toxicity of thiophosgene used in the reaction. Considering the above mentioned facts, there is a paramount interest to develop a practical and convenient synthesis for sugar-based oxazolidine-2-thiones under mild reaction condition.

Therefore, in continuation of our previous experience on conjugation of sugars with diverse scaffolds [37–48], herein we report a one-pot facile, controlled and selective synthesis of oxazolidine-2-thiones and thiazolidine-2-thiones from the corresponding glycosyl azides expecting for the notable efficacy for problematic bacteria, viruses and enzymes.

2. Results and discussion

Although 1,3-oxazolidine-2-thiones can be accessed in good yield from corresponding amino alcohols, but usually requires multi-steps reactions, low reaction yield, difficult purification process and thus incorporation of this bi-functionality on carbohydrates is still a challenge. Therefore, we bestowed our effort for the desired synthesis by utilizing glycosyl azido alcohols which is easy to prepare without any problematic issue from readily available starting material and moreover known for their excellent reactivity with triphenylphosphene. Our synthetic strategy begins with common monosaccharides (D-glucose, D-Mannose and D-Galactose) which were converted to corresponding sugar azido-alcohols (**3a-c**) *via* straightforward and high-yielding synthetic steps including isopropylidene protections followed by reacting with epichlorohydrin and their respective azidation [44–46]. To get a series of an another related sugar-based azido alcohols (**3d-l**), D-glucose and D-Mannose, both were subjected first isopropylidene protection followed by selective deprotection, then selective tosylation and finally their respective azidation reaction under standard reaction conditions (Scheme 2) [46].

The resulting glycosyl 1,2-azidoalcohols (**3a-l**) having both azido and hydroxyl functionality at vicinal carbons were obtained as a most suitable precursors for the required synthesis of 1,3-oxazolidine-2-thione (**4a-l**) *via in situ* formation of glycosyl isothiocyanate intermediate. For establishing the reaction condition, initially we treated compound **3a** (1.0 equiv) with PPh_3 (1.2



Scheme 2. Synthesis of glycosylated azido alcohols **3a-l** from various monosaccharides (D-Glucose, D-Mannose and D-Galactose).