Synthesis of higher carbon sugars thio-functionalized with heterocycles

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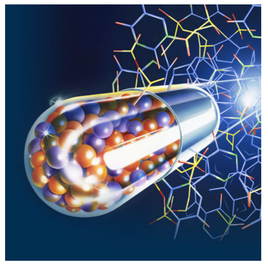


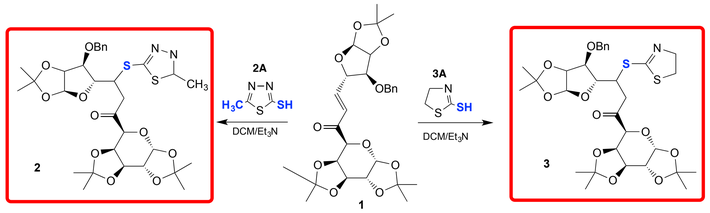
Abstract

In continuation of our studies on thio-functionalization of conjugated sugar systems[1], we expanded the original protocol to include higher carbon sugars[2].

The starting galactose enone **1** was synthesized according to the literature protocol[3] from galactose aldehyde. The base catalyzed Michael conjugate addition of heterocyclic thiols to enone **1** was performed by base catalysis such as, Et_3N, DABCO, and Hunig base in dichloromethane or chloroform. The highest yields were achieved with Et_3N as a catalyst in dichloromethane at room temperature for 48 hours.

The crystalline products **2** and **3** were isolated in 65% and 72% yield respectively and characterized by ^1H and ^{13}C NMR analysis.

Both thio-functionalized products **2** and **3** are of interest as new biological pharmacophores with potential antimicrobial activity against Gr (-) pathogens.



Scheme 1

Our successful synthesis of the first analogs of five membered exo-cyclic enones[1] prompted us to expand the scope of the reaction by using other heterocyclic thiols. All three representative substrates are characterized with a distinctive level of increased aromaticity and reactivity with biological and pharmacological activities. This specific combination of chemical/biological properties additionally constitute important rationale to pursue the expansion of the project.

Introduction

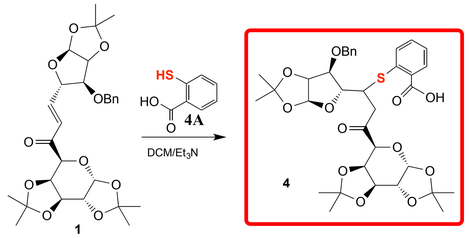
Enones and their linear sugar analogs of chalcones have attracted extremely wide attention as convenient probes for enzyme inhibition studies[4-6]. Recent evidence suggests that these derivatives may have therapeutic potential[7] and have been recently the subjects of great interest for their interesting pharmacological activities. They contain two aromatic rings with an unsaturated chain. Many biological activities have been attributed to this group, such as antitumoral,[8] anticancer and antioxidant,[9] antifungal,[10] antimitotic,[11] chemoprotective,[12] anti-inflammatory,[13] antimicrobial,[14] and antibacterial[15-16] activities. Some other functionalized *exo*-cyclic enones are involved with thioredoxin reductase (TrxR). Thioredoxin (Trx) is one of the major biological antioxidants regulating the cellular redox balance. This enzyme system, consisting of thioredoxin reductase (TrxR) with selenocysteine, is overexpressed in many human tumors and is recognized as a potential target for cancer therapy.

Additionally, aldose reductase (ALR2) catalyzes the conversion of glucose to sorbitol, which is the first step in the polyol pathway of glucose metabolism. Two of exo-cyclic analogs Isoliquiritigenin and butein have also exhibited ALR2 inhibitory activities in biochemical assays and inhibited sorbitol accumulation *in vivo*.

Methods

General method for the preparation of thio-adducts 2, 3 & 4

To a solution of enone (**1**) 1.28g (0.01mole) in 30 mL of dichloromethane a 0.01 mole of the respective thiols **2A, 3A and 4A** was added and magnetically stirred for 5.min. After that time, 0.5 mL of triethylamine was added drop-wise and the solution was stirred for 16-48hr. Upon overnight cooling at 5° C the crystalline residue was filtered off and dried on fresh air.



Scheme 2

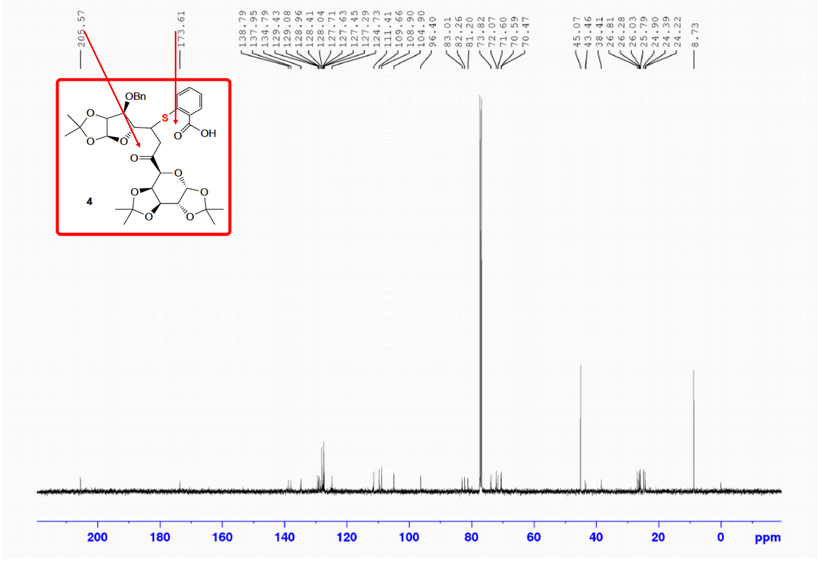
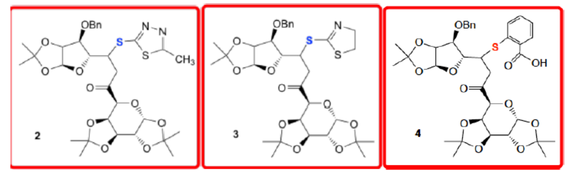


Fig. 1. ^{13}C NMR spectra of thio-functionalized enone 4

Table 1. Physical characteristic of *S-thio-adducts* **2, 3 & 4** .



Thio-adducts	m.p. °C	yield %	R_f^a	$[\alpha]_D$ (CH_2Cl_2)
2	178-180	70	0.87	--
3	85-87	62	0.76	-226.12
4	139-141	89	0.68	-203.21

Conclusion

We synthesized thio-adducts *via* stereoselective Michael reaction addition.

1. **The structures of thio-adducts were confirmed by the NMR spectroscopy.**
2. **In the case of thio-salicylic acid, (with o-SH group) a single adduct product was obtained is good 89% yield.**
3. **Other heterocyclic thiols produced *thio-adducts* in 65% and 72% yields.**
4. **The preliminary biological tests of all synthesized thio-adducts 2-4 are under investigations.**

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