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Synthesis, antifungal activities, and potential detoxification of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiocarbamates

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ABSTRACT

A series of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiocarbamates were synthesized by the reaction of glucosyl isothiocyanates with monohydric and dihydric alcohols, and acetone oxime, using methods of both normal reaction and microwave-assisted synthesis. Antifungal activities of the title compounds were determined with three kinds of plant pathogenic fungi, *Fusarium graminearum*, *Rhizoctoria cerealis*, and *Colletotrichum orbiculare*. The synthesized glucosyl thiocarbamates easily reacted with $HgCl_2$ to give novel metal–organic compounds, bis[*O*-alkyl *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiocarbamato]mercury, in yields of 80%. This strong affinity of thiocarbamates for mercury showed their potential utility in medical or marine environmental detoxification.

1. Introduction

Thiocarbamates are remarkable for their biological activities and are widely used as bactericides,[1–3] pesticides,[4,5] and herbicides.[6–9] Many of the thiocarbamates that have been reported are *N*-alkyl[10] and *N*-phenyl or benzyl[11] compounds, few of which are *N*-glucosyl.[12,13] The linkage between the hydrophobic tail and the sugar head in *N*-glucosyl thiocarbamates appears to modify the physicochemical properties of non-ionic surfactants by changing their water solubility.[13] As was reported, many biologically important products have a sugar unit joined through an atom (O, S, N, or C) or a group of atoms.[14] Glucosyl isothiocyanates, proven to be excellent intermediates, have been used for the preparation of a variety of carbohydrate derivatives of synthetic, biological, and pharmaceutical interest,[15,16] since they easily undergo many important reactions, such as cycloadditions and nucleophilic additions.[17]

Furthermore, thiocarbamates and some metal atoms (such as rhodium, iridium, palladium, platinum, and gold) could form the metal complexes.[18] Some thiocarbamates can be used as sulfhydryl group antidotes, and these compounds may have potential utility in medical or marine environmental fields,[19] owing to their high affinity to heavy metal cations,[20] for example, Hg^{2+} and Pb^{2+}. Hg-related health risks do exist for consumers of bivalves.[21] Also some thiocarbamates can be used as reagents in ore flotation, since their strong affinity and good selectivity for certain ions.[22] For example, *O*-isopropyl-*N*-ethylthiocarbamate is more selective for copper sulfide against gangue iron sulfides; thus, it can perform copper/iron separation.[23]

The reports about D-glucopyranosyl thiocarbamates are quite infrequent, and only a few of them have been described in detail.[12,13] In this study, 20 different *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiocarbamates were synthesized by the reaction of 2,3,4,6-tetra- *O*-acetyl-β-D-glucopyranosyl isothiocyanate with the compounds linking with one or two hydroxyl groups, respectively (Scheme 1). Their antifungal activities against three plant pathogenic fungi were evaluated. Furthermore, the potential utility of these glucosyl thiocarbamates for detoxification was investigated by reacting with $HgCl_2$.

2. Results and discussion

2.1. The synthesis of glucosyl thiocarbamates

Glucosyl isothiocyanates were synthesized in moderate yield by the reaction of an acylated glucosyl bromide with lead thiocyanate according to the literature,[24–28] and the acylated glucosyl bromide was prepared by methods described in the literature.[29,30] Glucosyl isothiocyanates reacted with the acyclic and heterocyclic monohydric alcohols to give the thiocarbamates **2a**–**2j** and **2m,** for the most part, in yields of over 80%, except for **2n** and **2o**, which were obtained by the reaction of glucosyl isothiocyanates with 1-(hydroxymethyl)-1*H*-1,2,4-triazole and acetoxime, respectively.

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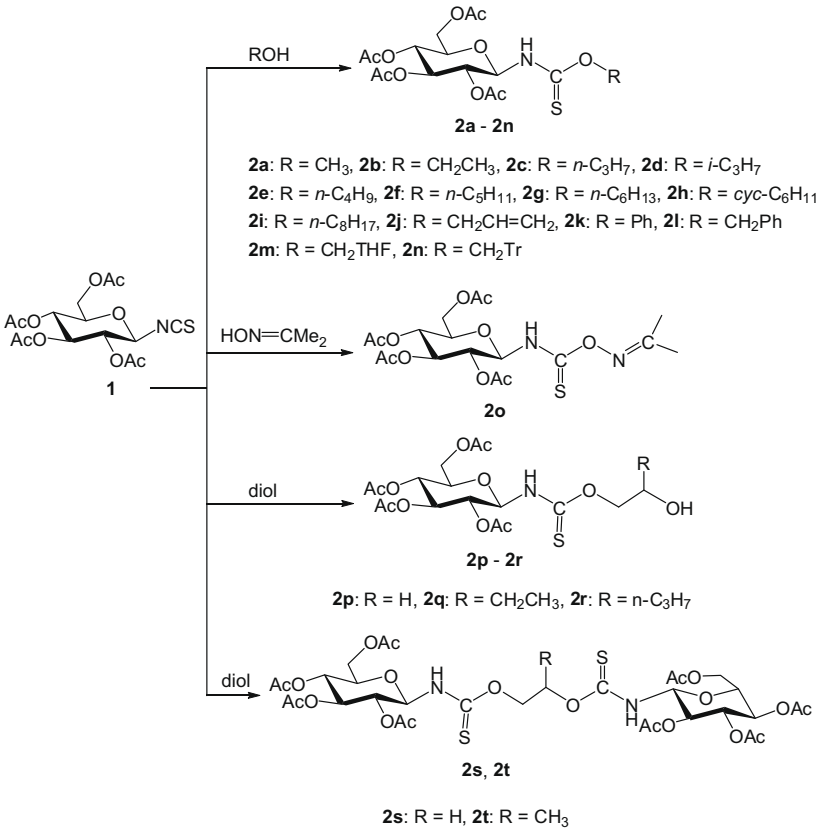
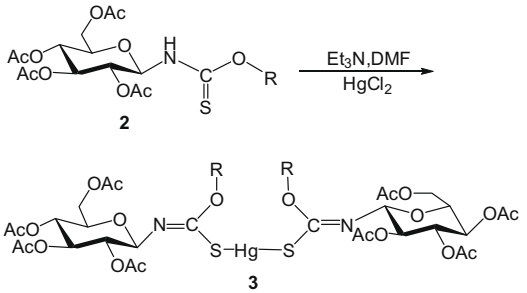


Scheme 1. Preparation of the title compounds.

However, phenol and benzyl alcohol were more difficult to react with the glucosyl isothiocyanates owing to their easy oxidation at high reaction temperatures (100 °C) and long reaction times (5 h). To limit the oxidation, microwave-assisted synthesis was used, and compounds **2k** and **2l** were obtained. In the reaction of glucosyl isothiocyanates with dihydric alcohols, monothiocarbamates **2p**–**2r**, which are linked with only one glucosyl group, with the other hydroxyl group left open, as well as the bridged bisthiocarbamates **2s** and **2t**, which are linked with two glucosyl groups, were prepared (Scheme 1). In preparation of monothiocarbamates **2p**–**2r**, the molar ratio of diols and *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)isothiocyanates was 2:1, while in preparation of the bisthiocarbamates **2s** and **2t**, the ratio of two reactants was just the opposite.

Compounds with the general structure **2** were characterized by IR, ^{1}H, and ^{13}C NMR spectroscopy and by elemental analysis. In the IR spectrum an absorbance at about 3300 cm^{-1} showed the presence of an NH group, and the absorbance at about 1520 cm^{-1} indicated the NH(C=S) group. In the ^{1}H NMR spectra the NH of monothiocarbamates appeared as doublet at δ 6.16–7.03 , while the NH of bisthiocarbamates appeared as broad peak at δ 7.08. H-1, H-2, H-3, and H-4 appeared as doublet of doublets (overlapped to appear as three-line patterns), respectively, while H-6a and H-6b appeared as two-line patterns. As a result of the complex coupling with H-4, H-6a and H-6b, H-5 appeared as a multiplet. In the ^{13}C NMR spectra, the C=S of *N*-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiocarbamates appeared at about δ 191–192, and four acetyl C=O groups on the glucosyl ring appeared at about δ 169–171. C-1 appeared at about δ 83, C-2–C-6 appeared at about δ 61–73. The elemental analysis data were in accord with the structure of compounds **2**.



3a: R = CH_3, **3b**: R = CH_2CH_3, **3c**: R = *n*-C_3H_7, **3d**: R = *i*-C_3H_7, **3e**: R = *n*-C_4H_9
3f: R = *n*-C_5H_{11}, **3g**: R = *n*-C_6H_{13}, **3h**: R = *cyc*-C_6H_{11}, **3i**: R = *n*-C_8H_{17}

Scheme 2. Reaction of the thiocarbamates with $HgCl_2$.

2.2. Antifungal activities of glucosyl thiocarbamates

Antifungal activities of compounds **2** against three kinds of plant pathogenic fungi (*Fusarium graminearum*, *Rhizoctoria cerealis*, and *Colletotrichum orbiculare*) were evaluated by a radial growth inhibition technique with three repeats for each sample according to the literature procedure.[31] As shown in Table 1, most of compounds **2** showed weak antifungal activities at 500 μg mL^{-1}, but some of the compounds, such as **2c**, **2f**, **2s**, and **2t** exhibited somewhat stronger antifungal activities. It is interesting that there might be certain relationship between antifungal activities and the number of carbon atoms in the alcohol position of compounds **2** synthesized by straight-chain fatty alcohols, that is, compounds **2a**, **2c**, and **2f** with odd-numbered carbon atoms have stronger antifungal activities than compounds **2b**, **2e**, and **2g** with even-numbered carbon atoms. By comparing **2s** and **2t** with **2p**,