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Expeditious synthesis of cyclic isourea derivatives of β-D-glucopyranosylamine

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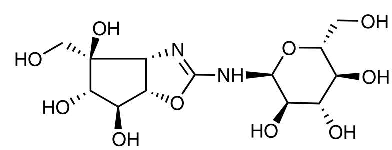
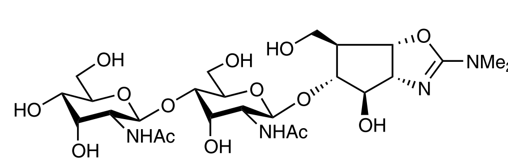
Abstract—2-(Alkylamino, dialkylamino, arylamino)tetrahydropyrano[2,3-*d*]oxazoles are prepared in good yield by a one-pot three-step synthesis from *O*-unprotected β-D-glucopyranosylamine, by its transformation into glucopyranosyl isothiocyanate in dioxane–water, coupling with amines, and reaction of the corresponding thioureas with yellow mercury(II) oxide in the same reaction medium. In the case of diethylamine prolonged reaction time during the last step, with an extra portion of yellow HgO, led to *N*,*N*-diethyl-*N*′-(β-D-glucopyranosyl)urea in a one-pot four-step synthesis. 2-(β-D-Glucopyranosylamino)tetrahydropyrano[2,3-*d*]oxazole, an analogue of trehazolin, is obtained in good yield by cyclocondensation of 1,3-bis(β-D-glucopyranosyl)thiourea.

2-Amino-2-oxazolines have received considerable attention due to their interest as biological active molecules, which show adrenergic,[1] octapamine,[2] imidazoline[3] receptor agonist activity as well as histamine receptor antagonist,[4] and may be useful for the treatment of hypertension and glaucoma, and as specific inhibitors of pheromone biosynthesis. Among the methods to prepare 2-amino-2-oxazolines, cyclodesulfurization of conveniently hydroxylated thiourea derivatives with lead(II) oxide,[5] yellow mercury(II) oxide,[2b,6] 2-chloro-3-ethylbenzoxazolium tetrafluoroborate,[7] superoxide radical anion,[8] *p*-toluenesulfonyl chloride/NaOH,[9] or MeI/lutidine[10] have been used.

In the carbohydrate field, natural *N*-substituted cyclic isourea derivatives of aminocyclitols have been found to display potent and selective inhibitory effects on a variety of glycosidases. Examples include trehazolin **1**[11] and allosamidin **2**,[12] potent inhibitors of trehalase and chitinase, respectively. This led to intensive research on the total synthesis of **1**, **2**, and structural analogues which contain the chemically modified cyclitol or sugar portion.[13–15] The syntheses of trehazolin analogues wherein the aminocyclopentitol ring has been replaced either by a six-membered polyhydroxylated carbocycle[16–18] or by a tetrahydropyran unit[19] have been reported. Syntheses of tetrahydrofurano[2,3-*d*]oxazoles from *cis*-fused cyclic sugar thiocarbamates by sequential *S*-*p*-chlorobenzylation and nucleophilic displacement of the *p*-chlorobenzylthio group with amines have been undertaken by Pinter's group.[20]



1 Trehazolin



2 Allosamidin

We now report the in situ preparation of 2-aminotetrahydropyrano[2,3-*d*]oxazoles **7a**–**g** from β-D-glucopyranosylamine **3**[21] in a one-pot three-step procedure. Treatment of **3** with thiophosgene in 1:1 water/dioxane buffered with $NaHCO_3/CO_2$, followed by addition of several amines, as described recently,[22] and finally, treatment in the same flask with yellow mercury(II)

Keywords: thiourea desulfurization; cyclizations; mercury(II) oxide; isoureas; ureas; trehazolin.

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oxide (3 equiv.) for 1–3 h at room temperature, led to **7a**–**g** (Scheme 1). These compounds were isolated in 50–70% yield after silica gel column chromatography (Table 1).[23] Bola-amphiphile[24] **7f** was purified by crystallization from ethanol. This method when applied to polar amines, such as taurine or β-D-glucopyranosylamine, also gave the expected cyclic isoureas as the main compounds as deduced by the ^{1}H NMR of the crude reaction mixture; however, purification by silica gel or gel filtration chromatography led to extensive decomposition. Use of commercial yellow HgO for the cyclodesulfurization of thioureas in aqueous dioxane, buffered with $NaHCO_3/CO_2$ containing minor amounts of amines, contrasts with the use of isolated sugar thioureas and freshly prepared and dried mercury(II) oxide[25,26] in solvents such as dried THF,[25] Et_2O,[27] MeCN,[28] Et_2O/Me_2CO[17,29] or $EtOH/Me_2CO$.[26] Similarly, Mukaiyama's method of thiourea cyclization[7a] is carried out with 2-chloro-3-ethylbenzoxazolium tetrafluoroborate in dried MeCN under N_2.[19,30] Our results indicate that the proposed transient carbodiimides should react faster with the adjacent *trans*-hydroxy group to construct cyclic isoureas, than with water molecules to form ureas.

In the case of diethylamine, in situ treatment of **6e** with 3 equiv. of yellow HgO for 2 h gave isourea **7e** together with urea **9** in 70 and 18% yield, respectively, after column chromatography. When **6e** was in situ treated with two portions of yellow HgO (3 equiv. each) for 4 h, complete conversion of **7e** into urea **9** was observed (85% isolated yield).[31] When this procedure was applied to the transformation of *N*-butyl and tolyl isoureas **7a** and **7c** to the corresponding ureas, no significant conversion of the starting materials was observed on prolonged reaction times (48 h) at room temperature. The formation of **9** might be explained through the transient carbodiimide derivative **8** (Scheme 1). Other methods to convert cyclic isoureas into ureas have previously been reported,[32,33] and conversion of thioureas directly into ureas have also been described.[14d,34,35]

We also report the synthesis of trehazolin analogue **7h**[36] in 89% yield by treatment of symmetrical *O*-unprotected *N*,*N*′-bis(β-D-glucopyranosyl)thiourea **6h**[22] with yellow mercury(II) oxide (3 equiv.) in 1:1 water/dioxane for 3 h. No formation of urea was detected. Similarly, 2-octyl and *p*-tolylaminooxazolines **7b** and **7c** were prepared from thioureas **6b** and **6c** in 75 and 94% yield, respectively, using methanol as solvent. Synthesis of **7h** has previously been reported by Shiozaki[19] by hydrogenolysis of the derivative of **7h** tetra-*O*-benzylated in the glucopyranose unit, which was prepared from per-*O*-acetylated and per-*O*′-benzylated *N*,*N*′-bis(β-D-glucopyranosyl)thiourea, following a sequence of Zemplén deacetylation and cyclodesulfurization using Mukaiyama's method. The reported hydrogenolysis with $Pd(OH)_2$-on-charcoal gave[19] an inseparable mixture of **7h** (17%) and *N*,*N*′-bis(β-D-glucopyranosyl)urea (32%).

In conclusion, we have developed a versatile and expeditious three-step one-pot synthetic route to transform primary or secondary amines into tetrahydropyrano-[2,3-*d*]oxazoles starting from the easily available β-D-glucopyranosylamine **3**. The protection–deprotection steps are avoided, simplifying the synthetic route with good overall yields. We have proved that cyclodesulfurization of glycosyl thioureas with yellow HgO can be carried out in aqueous dioxane or in methanol, and in the case of diethylamine conversion of cyclic isourea into urea was achieved.

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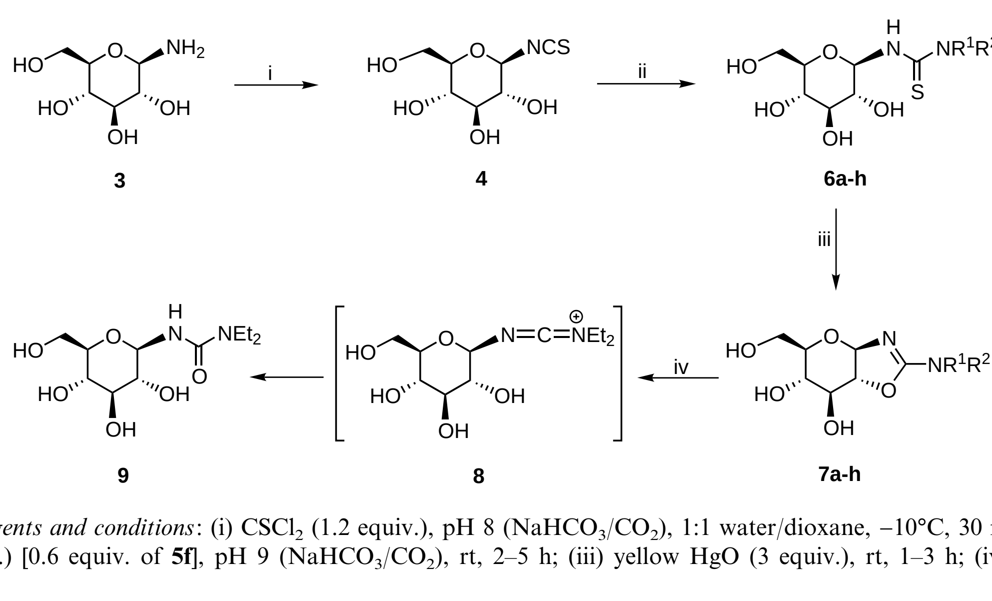
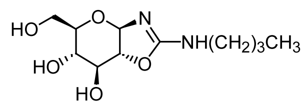
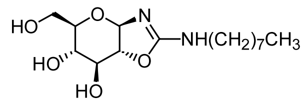
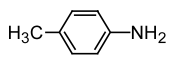
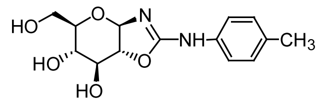
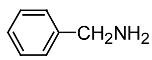
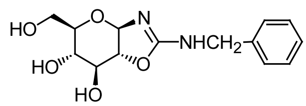
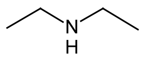
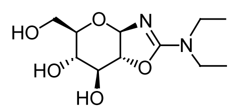
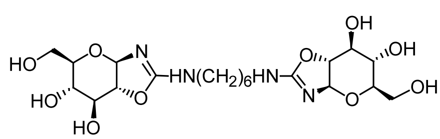
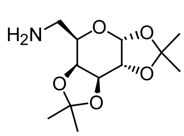
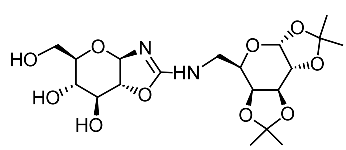
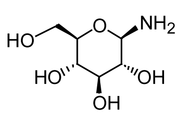
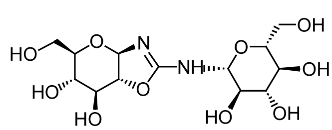


Scheme 1. *Reagents and conditions*: (i) $CSCl_2$ (1.2 equiv.), pH 8 ($NaHCO_3/CO_2$), 1:1 water/dioxane, −10°C, 30 min; (ii) R^1R^2NH **5a**–**h** (1.2 equiv.) [0.6 equiv. of **5f**], pH 9 ($NaHCO_3/CO_2$), rt, 2–5 h; (iii) yellow HgO (3 equiv.), rt, 1–3 h; (iv) yellow HgO (3 equiv.), rt, 2 h.

Table 1. Synthesis of tetrahydropyrano[2,3-*d*]oxazoles **7a**–**h** from β-D-glucopyranosylamine **3**

R^1R^2NH	**5**	Products		Yield (%)[a]	(%)[b]
$CH_3(CH_2)_3NH_2$	**5a**		**7a**	67	-
$CH_3(CH_2)_7NH_2$	**5b**		**7b**	50	75
	**5c**		**7c**	69	94
	**5d**		**7d**	57	-
	**5e**		**7e**	70	-
$H_2N(CH_2)_6NH_2$	**5f**		**7f**	58	-
	**5g**		**7g**	59	-
	**5h**		**7h**	-	89

[a]Isolated yields from **3**.
[b]Isolated yields from **6**.

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36. Selected data for **7h**: $[\alpha]_D^{22}$ +28° (*c* 0.5, H_2O); IR ν_{max} 1659 cm^{-1}; ^1H NMR (500 MHz, D_2O): δ aglycon part 4.89 (d, 1H, $J_{1,2}$ 9.8 Hz, H-1′), glucopyranosyl part 4.72 (d, 1H, $J_{1,2}$ 8.9 Hz, H-1) ppm; ^{13}C NMR (125.7 MHz, D_2O): δ aglycon part 163.6 (CN), 95.2 (C-1′); glucopyranosyl part 84.3 (C-1) ppm. HRFABMS calcd for $C_{13}H_{22}NaN_2O_{10}$ $[M+Na]^+$ 389.1172, found 389.1185.