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Synthesis of *O*-unprotected glycosyl selenoureas. A new access to bicyclic sugar isoureas

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Abstract—β-D-Gluco and mannopyranosyl selenoureas have been prepared by coupling of the corresponding glycosylamines with phenyl isoselenocyanate in aqueous pyridine. Alkyl and aryl isoselenocyanates, and 1,4-phenylene diisoselenocyanate have been obtained from the corresponding formamides with an excess of triphosgene, black selenium and triethylamine. Treatment of the *O*-unprotected β-D-glucopyranosyl selenourea with aqueous oxygen peroxide afforded a 1,2-*trans*-fused bicyclic isourea.

The interest in the chemistry of organoselenium compounds has increased remarkably in the last few decades due to their synthetic applications[1] and biological activities.[2] Selenoureas, useful for the synthesis of selenium-containing heterocycles,[3] have been prepared by different methods: diamino carbenes and selenium,[4] carbodiimides and LiAlHSeH,[5] cyanamides and H_2Se,[6] carbon diselenide and amines[7] or ureas and bis(trimethylsilyl)selenide.[8] However, the preparation of selenoureas is mainly carried out by reaction of isoselenocyanates with amines.[9,10]

Much effort has been devoted to the preparation of sugar ureas[11] and thioureas;[12] on the contrary, we have found only one report on the synthesis of sugar selenoureas.[13] Sensitivity towards oxidation or light of selenium containing compounds,[14] together with the difficulties in preparing alkyl and aryl isoselenocyanates, may explain the scarce development of the chemistry of sugar selenoureas, compared with that of their urea and thiourea counterparts.

We now report the preparation of β-D-glycopyranosyl selenoureas of *gluco* and *manno* configurations **13** and **14** by reaction of the corresponding β-D-glycopyranosylamines with phenyl isoselenocyanate in aqueous pyridine in a 75% and 62% yield, respectively.

Phenyl isoselenocyanate and other alkyl and aryl isoselenocyanates were prepared starting from the corresponding formamides[15] (Scheme 1), following a modification of Barton et al's procedure.[16] We have used solid triphosgene,[17] instead of phosgene, in the one-pot dehydration of the formamides **1**–**5** in toluene containing triethylamine, followed by reaction of the nonisolated isocyanides with an excess of selenium black (Scheme 1, method A). This gave isoselenocyanates **6**–**10** (Table 1, method A) in 16–75% yields.

The low yield observed for the hitherto unknown 1,4-phenylene diisoselenocyanate **9** could be explained by the extensive polymerization[18] of the 1,4-phenylene diisocyanide **4** during the prolonged heating in toluene. However, the yields were improved considerably (69–85%, Table 1, method B) when we used refluxing dichloromethane (Scheme 1, method B) instead of toluene, as the lower temperature reaction could prevent the 1,4-phenylene diisocyanide polymerization.[19] Another modification of Barton's procedure to prepare isoselenocyanates has recently been reported.[20]

Compounds **13** and **14** (Scheme 2) are the first examples of *O*-unprotected β-D-glycopyranosyl selenoureas[21] and were conventionally acetylated to afford penta-acetylated derivatives **15** and **16**. It is noteworthy that the acetylation of the selenourea moiety was completely regioselective, as only the nitrogen bearing the phenyl group was acylated, despite the conjugation between the nitrogen lone pair and the aromatic ring. Reaction did not take place in the nitrogen bound to the sugar ring, possibly due to steric hindrance.

Keywords: Isoselenocyanates; Selenoureas; Isoureas; Triphosgene; Selenium; Hydrogen peroxide.
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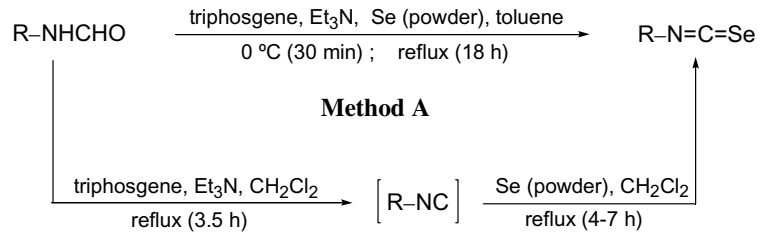
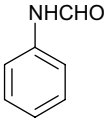
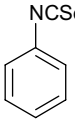
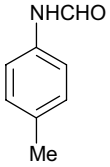
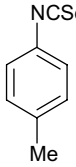
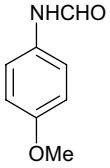
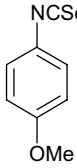
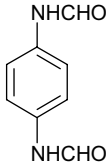
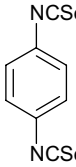
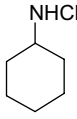
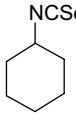


Scheme 1.

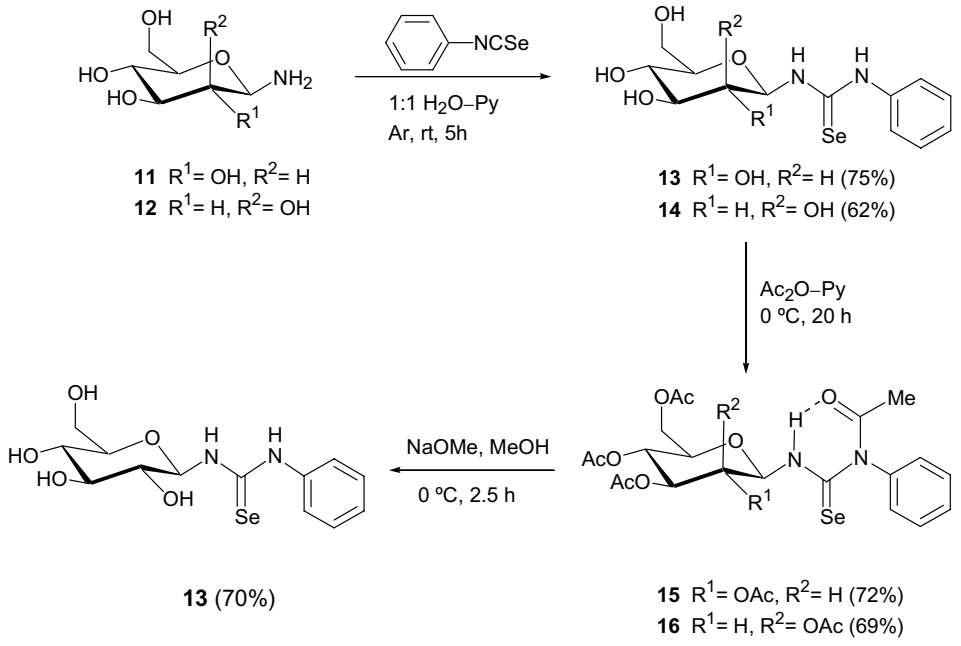
Table 1. Synthesis of alkyl and aryl isoselenocyanates from *N*-substituted formamides

R–NHCHO	Compound	R–N=C=Se	Compound	Method A, yield (%)	Method B, yield (%)
	**1**		**6**	67	75
	**2**		**7**	55	88
	**3**		**8**	52	77
	**4**		**9**	16	80
	**5**		**10**	75	69

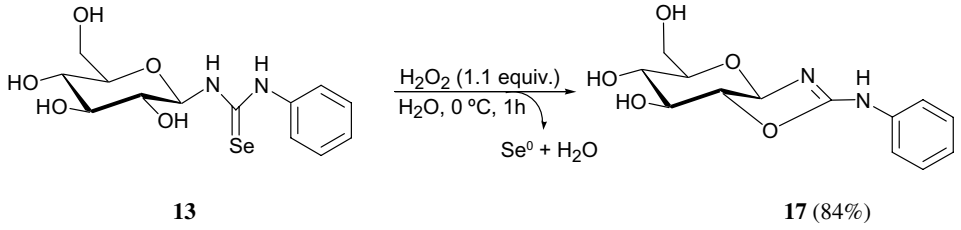
^{1}H NMR spectra of compounds **15** and **16** showed signals corresponding to the NH protons as doublets at 12.49 and 10.68 ppm, respectively. The strong deshielding of these protons is in agreement with the existence of the hydrogen bonding NH···O=C–N. The coupling constants $^3J_{\text{H-1,NH}}$ (7.7 Hz for **15** and 8.0 Hz for **16**) confirm where the *N*-acetylation took place and suggest the *anti-Z,E* conformation shown in Scheme 2.

To our knowledge, the only reported per-*O*-acetylated β-D-glycopyranosyl selenoureas were prepared by Witczak,[13] by reaction of fully *O*-protected glycopyranosyl isoselenocyanates with aniline. He also described that attempts to prepare free glycosyl selenoureas by deacetylation under Zemplén conditions using catalytic sodium methoxide were unsuccessful, and decomposition with precipitation of elemental selenium was observed. However, in our hands, treatment of glucopyranosyl selenourea **15** with methanolic sodium methoxide at 0 °C gave **13** in a 70% yield, without appreciable decomposition (Scheme 2).

Compounds **13** and **14** underwent slow decomposition by sunlight, with precipitation of elemental selenium and formation of new compounds. In the case of glucopyranosyl selenourea **13**, the formation of bicyclic isourea **17**[22] was detected as the only compound formed and this transformation was accelerated by addition of hydrogen peroxide (1.1 equiv) and completed in 1 h at 0 °C in an 84% yield (Scheme 3). This reaction can be considered as a new procedure to prepare cyclic isoureas; other methods for the preparation of cyclic isoureas involve the cyclodesulfuration of conveniently hydroxylated thiourea derivatives with Mukaiyama's



Scheme 2.



Scheme 3.

reagent,[23] *p*-toluenesulfonyl chloride/NaOH[24] or MeI/lutidine.[25] Our results contrast with those reported by Treppendahl,[26] who described the oxidation of *N*,*N*′-diphenylselenourea with H_2O_2 to give a benzoselenazoylguanidine (a selenoanalogue to Hugershoff's base) and a cyclic dimer of the corresponding carbodiimide. Oxidation of selenoureas with $NaIO_4$ in refluxing DMF to give carbodiimides has recently been reported.[9]

The structure of **17** was confirmed by comparison of its ^1H and ^{13}C NMR data with those of other bicyclic isoureas previously prepared by us from *O*-unprotected β-D-glucopyranosyl thioureas by treatment with yellow HgO.[27] Treatment of the mannopyranosyl selenourea **14** with hydrogen peroxide under the above described conditions led to a nonresolved mixture of unidentified compounds, maybe due to the less stability of five-membered–six-membered *cis*-fused bicyclic isoureas.[28] The mild oxidation of glycopyranosyl selenoureas with hydrogen peroxide suggests that they may be used as antioxidant agents.[29]

In conclusion, we have developed a practical procedure for the preparation of unprotected glycopyranosyl selenoureas and their mild transformation into bicyclic isoureas. Furthermore, we have proved that the preparation of alkyl and aryl isoselenocyanates, and 1,4-phenylene diisoselenocyanate following Barton's procedure is improved by using triphosgene instead of phosgene and dichloromethane instead of the less polar toluene.

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15. General procedure for the preparation of isoselenocyanates. Method A: to a mixture of formamides **1**–**5** (1.5 mmol), selenium powder (3.0 mmol) and triethylamine (6.0 mmol) in toluene (15 mL), at 0 °C under argon, was dropwise added a solution of triphosgene (1.0 mmol) in toluene (10 mL) for a period of 30 min. After the addition, the resulting mixture was refluxed for 16 h in the darkness and then it was filtered over Celite and the filtrate was purified by column chromatography (hexane–EtOAc gradient) to afford isoselenocyanates **6**–**10**. Method B: to a refluxing mixture of the formamides **1**–**5** (1.5 mmol), triethylamine (6.4 mmol) in CH_2Cl_2 (5 mL) and 4 Å molecular sieves was dropwise added a solution of triphosgene (0.8 mmol) in CH_2Cl_2 (2 mL) for a period of 1 h. After the addition, it was refluxed for 2.5 h and then, selenium powder (3.0 mmol) was added. The resulting mixture was refluxed for other 4–7 h; conventional work-up and column chromatography afforded isoselenocyanates **6**–**10**.
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21. For the preparation of **13**: To a solution of phenyl isoselenocyanate (244 mg, 1.34 mmol) in pyridine (2 mL), at rt under argon, was added a solution of β-D-glucopyranosylamine **11** (200 mg, 1.12 mmol) in water (2 mL). The reaction was kept in the darkness at rt for 5 h, concentrated to dryness and purified by column chromatography to afford **13** (302 mg, 75%). Selected data for **13**: $[\alpha]_D^{26}$ −19° (*c* 1.4, CH_3OH); IR ν_{max} 3317, 1545 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 5.61 (br s, 1H, H-1); ^{13}C NMR (75.5 MHz, CD_3OD) δ 182.8 (C═Se), 88.2 (C-1); HRFABMS calcd for $C_{13}H_{18}N_2NaO_5{}^{80}Se$ $[M+Na]^+$ 385.0279, found 385.0267.
22. For the preparation of **17**: To a solution of *N*-(β-D-glucopyranosyl)-*N*′-phenylselenourea **13** (26 mg, 0.07 mmol) in water (0.5 mL) at 0 °C was added 3.3% w/v hydrogen peroxide (0.076 mL, 0.07 mmol). The reaction was kept at that temperature for 1 h and then it was diluted with EtOH and filtered over Celite. The filtrate was concentrated to dryness and purified by column chromatography to give pure isourea **17** (17 mg, 84%). Selected data for **17**: $[\alpha]_D^{21}$ +85° (*c* 1.3, DMSO); IR ν_{max} 3341, 1647 cm^{-1}; ^1H NMR (500 MHz, CD_3OD) δ 4.85 (d, 1H, $J_{1,2}$ = 9.6 Hz, H-1); ^{13}C NMR (125.7 MHz, CD_3OD) δ 159.8 (C═N), 95.1 (C-1); HRFABMS calcd for $C_{13}H_{16}N_2NaO_5$ $[M+Na]^+$ 303.0957, found 303.0963.
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