Accepted Manuscript

Preparation of glycosyl thiourea derivatives from glycosyl azides using sulfamic acid and sodium iodide in one-pot

Arin Gucchait, Manas Jana, Kuladip Jana, Anup Kumar Misra

PII: S0008-6215(16)30284-1

DOI: 10.1016/j.carres.2016.09.002

Reference: CAR 7252

To appear in: *Carbohydrate Research*

Received Date: 2 August 2016

Revised Date: 2 September 2016

Accepted Date: 3 September 2016

Please cite this article as: A. Gucchait, M. Jana, K. Jana, A.K. Misra, Preparation of glycosyl thiourea derivatives from glycosyl azides using sulfamic acid and sodium iodide in one-pot, *Carbohydrate Research* (2016), doi: 10.1016/j.carres.2016.09.002.

Preparation of glycosyl thiourea derivatives from glycosyl azides using sulfamic acid and sodium iodide in one-pot

Arin Gucchait, Manas Jana, Kuladip Jana and Anup Kumar Misra*

Bose Institute, Division of Molecular Medicine, P-1/12, C.I.T. Scheme VII-M, Kolkata-700054, India

Abstract: Novel one-pot reaction conditions have been developed for the preparation of glycosyl thiourea derivatives directly from glycosyl azides mediated by a combination of sulfamic acid and sodium iodide. The reaction conditions were clean, non-toxic and the products were isolated in good to excellent yield.

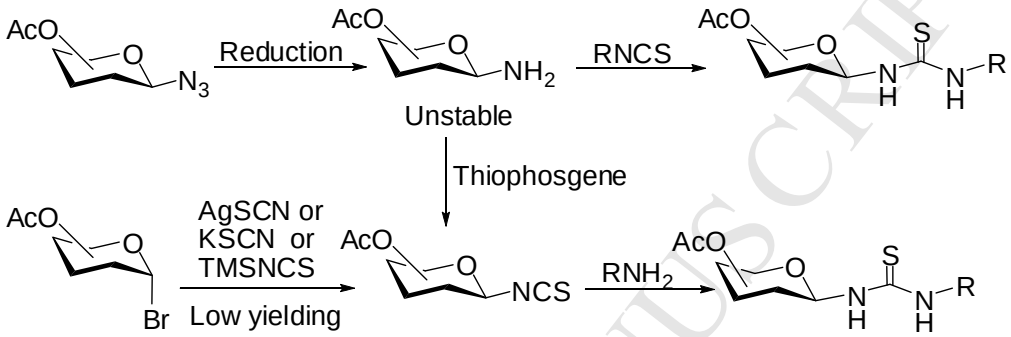
Keywords: Carbohydrate; azide; thiourea; reduction; sulfamic acid; sodium iodide; isothiocyanate.

1. Introduction

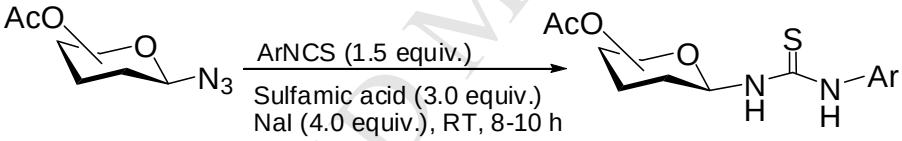
Thiourea derivatives are important class of molecules having versatile chemical and biological applications.[1] They have been used in therapeutics as antioxidant,[2] anti-bacterial,[3] anti-inflammatory,[4] anti-parasitic,[5] anti-HIV,[6] anti-tubercular,[7] rodenticide,[8] anti-cancer agents,[9] anti-fungal agents[10] etc. Thiourea derivatives have been used as agrochemicals such as insect growth regulator,[11] and herbicides.[12] They have also wide applications in the chemical synthesis of heterocycles and other organic molecules.[13,14] In the recent past, thiourea derivatives have been applied as organocatalysts and ligands in a variety of asymmetric organic reactions.[15,16] In addition, they have been applied as chemical sensors for the detection of heavy metals[17] and in polymer synthesis.[18]

Glycosyl thiourea derivatives have been used for the preparation of several biologically important molecules such as glycoconjugates,[19] thioureidosugar derivatives,[20] nucleosides,[21] spiroglycosides,[22] glycoclustures and dendrimers,[23] bridged thiourea calix sugar derivatives[24] etc. A number of glycosyl thiourea derivatives have been found promising as antiviral, antibacterial and antitumor agents.[25] Because of the increasing therapeutic importance, several glycosyl thiourea derivatives have been synthesized using the reaction of glycosyl isothiocyanates with aryl/alkyl amines or reaction of glycosyl amines with aryl/alkyl isothiocyanates (Scheme 1).[26-29] However, the reported methods for the preparation of glycosyl thiourea derivatives suffer from several shortcomings such as, handling of unstable glycosyl halide for the preparation of glycosyl isothiocyanate derivatives, chemical and thermal instability of glycosyl amine derived from the reduction of glycosyl azides, operational complication for the preparation of glycosyl amines,[27,29] poor yield in the thiophosgene mediated conversion of amino group into isothiocyanato group,[28] hazardous reaction conditions[29] etc. Therefore, there is a strong need to develop a high yielding, reproducible, user friendly reaction condition for the preparation of glycosyl thiourea derivatives. During our synthetic studies on carbohydrates we were interested to prepare a series of glycosyl thiourea derivatives. It was envisaged that development of a one-pot reaction condition for the reduction of azido group followed by reaction with an appropriate aryl/alkyl isothiocyanate could furnish satisfactory yield of the glycosyl thiourea derivative in a clean reaction condition. Prompted by a recent report of Shankaraiah et al.[30] for the preparation of podophyllotoxin-thiourea congeners, in which azide derivative was reacted with aryl isothiocyanates in the presence of a combination of sulfamic acid and sodium iodide, it was decided to prepare glycosyl thiourea derivatives directly from glycosyl azides avoiding the problems associated with the preparation of glycosyl amines or isothiocyanate derivatives. Earlier, sulfamic acid has been used in various organic transformations because of its organocatalytic property.[31] We report herein a convenient one-pot synthesis of glycosyl thiourea

conjugates by the reaction of glycosyl azides with aryl isothiocyanates in the presence of a combination of sulfamic acid and sodium iodide (Scheme 2). It is presumed that on treatment with a combination of sulfamic acid and sodium iodide, the glycosyl azide reduced to form glycosyl amine *in situ* which immediately reacts with aryl isothiocyanate to furnish glycosyl thiourea derivatives.



Scheme 1: Conventional approaches for the preparation of glycosylthiourea derivatives.



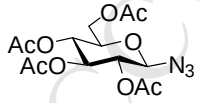
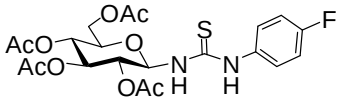
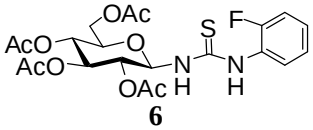
Scheme 2: Preparation of glycosyl thiourea derivatives directly from glycosyl azides.

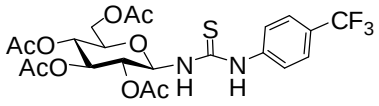
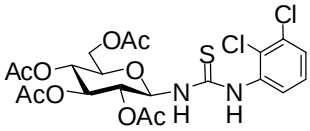
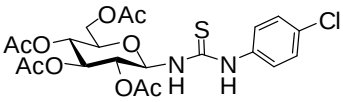
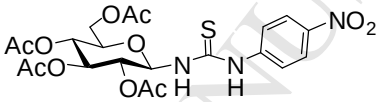
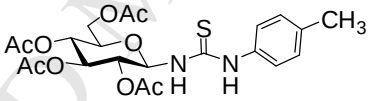
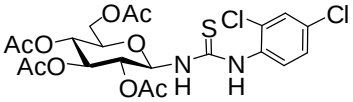
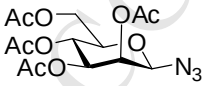
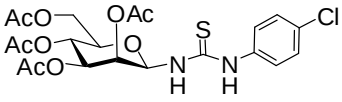
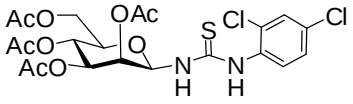
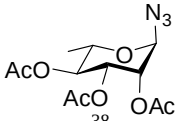
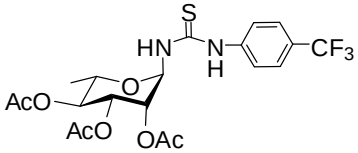
2. Results and discussion

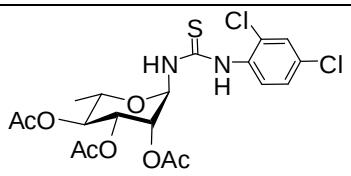
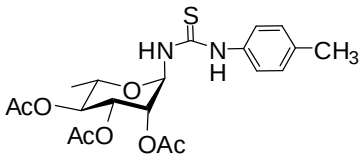
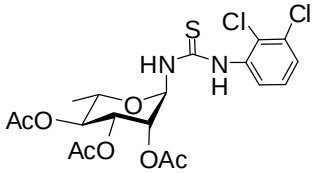
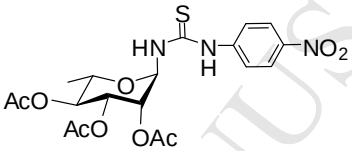
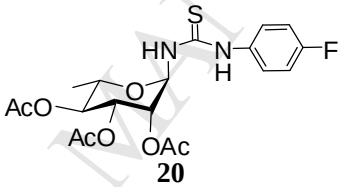
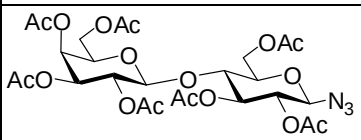
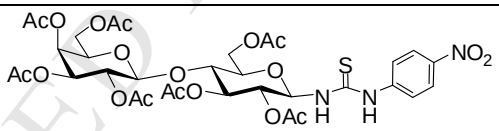
In a set of initial experiments, 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl azide (**1**) (1 mmol) was allowed to react with 4-fluoro-benzylisothiocyanate in the presence of a varied quantity of sulfamic acid and sodium iodide at room temperature in a variety of solvents such as, THF, CH_3CN, DMF etc. After a series of optimization, it was observed that use of 3.0 equiv. of sulfamic acid and 4.0 equiv. of sodium iodide in acetonitrile resulted in the formation of 4-fluorophenyl 3-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl) thiourea (**5**) in 70% yield in 8 h at room temperature. Following similar reaction condition a series of per-*O*-acetylated glycosyl azide derivatives were reacted with a series of aryl isothiocyanates to furnish a variety of per-*O*-

acetylated glycosyl aryl thiourea derivatives in very good yield (Table 1). Although in the earlier report less amount of reagents were used for this transformation, in this case reducing the quantity of sulfamic acid or sodium iodide led to incomplete conversion of the starting material even after 24 h presumably due to the fact that sodium iodide got decomposed under the reaction condition. A scaled up synthesis of compound **10** was also carried out with similar yield as in small scale preparation. All products were unambiguously characterized by their spectral analysis. In order to evaluate the medicinal potential of the compounds it is necessary to have their deprotected version. Therefore, representative thiourea derivatives (**10**, **12** and **16**) were subjected to the transesterification with dilute sodium methoxide following the reaction conditions reported by Somsak *et al*.[32] Gratifyingly, quantitative yield of de-O-acetylated thiourea derivatives were achieved without formation of any by product besides the possibility of the reactivity of thiourea functionality with sodium methoxide. Presumably, the azide group was reduced to amine functionality in the presence of the combination of sulfamic acid and sodium iodide, which reacted with aryl isothiocyanates to give the thiourea derivatives.

Table 1: Preparation of glycosyl thiourea derivatives by Sulfamic acid and Sodium iodide mediated reaction of glycosyl azides with aryl isothiocyanates in acetonitrile.

Sl. No.	Glycosyl azide	Product	Time (h)	Yield (%)	Ref
1	 **1**	 **5** m.p. 190-191 °C [EtOH]; $[\alpha]_D^{25}$ + 20 (*c* 1.0, $CHCl_3$); [Lit. m.p.: 191–193 °C; $[\alpha]_D$ +18 (*c* 0.29, $CHCl_3$)].	8	70	32
2	**1**	 **6** m.p. 187-188 °C [EtOH]; $[\alpha]_D^{25}$ + 16 (*c* 1.0, $CHCl_3$).	8	70	33

3	**1**	 **7** m.p. 110-112 °C [EtOH]; $[\alpha]_D^{25}$ + 28 (*c* 1.0, $CHCl_3$); [Lit. m.p.: 112–114 °C; $[\alpha]_D$ +32 (*c* 0.15, $CHCl_3$)].	8	72	32
4	**1**	 **8**	9	66	--
5	**1**	 **9** m.p. 127-128 °C [EtOH]; $[\alpha]_D^{25}$ – 10 (*c* 1.0, $CHCl_3$); [Lit. m.p.: 128–130 °C; $[\alpha]_D$ – 12.3 (*c* 1.8, $CHCl_3$)].	8	68	34
6	**1**	 **10** m.p. 96-98 °C [EtOH]; $[\alpha]_D^{25}$ + 16 (*c* 1.0, $CHCl_3$)	8	74 72 (5 g scale)	33
7	**1**	 **11** m.p. 76-78 °C [EtOH]; $[\alpha]_D^{25}$ – 4 (*c* 1.0, $CHCl_3$)	10	56	35
8	**1**	 **12** m.p. 176-178 °C [EtOH]; $[\alpha]_D^{25}$ – 14 (*c* 1.0, $CHCl_3$); [Lit. m.p.: 178 °C].	8	62	36
9	 **2**	 **13** $[\alpha]_D^{25}$ – 6 (*c* 1.0, $CHCl_3$)	8	65	37
10	**2**	 **14**	8	60	--
11	 **3**[38]	 **15**	8	68	--

12	**3**	 **16**	8	58	--
13	**3**	 **17**	10	58	--
14	**3**	 **18**	10	62	--
15	**3**	 **19**	8	76	--
16	**3**	 **20**	8	64	--
17	 **4**	 **21**	10	68	--

3. Conclusion

In summary, a straightforward convenient one-pot reaction condition has been developed for the preparation of glycosyl thiourea derivatives in excellent yield directly from glycosyl azides mediated by a combination of sulfamic acid and sodium iodide avoiding the use of toxic reagents. Further utilization of glycosyl thiourea derivatives in the organic transformations are in progress in our laboratory.

4. Experimental

4.1. General methods: All reactions were monitored by thin layer chromatography over silica gel coated TLC plates. The spots on TLC were visualized by warming ceric sulphate (2% $Ce(SO_4)_2$ in 2N H_2SO_4) sprayed plates in hot plate. Silica gel 230-400 mesh was used for column chromatography. ^1H and ^{13}C NMR spectra were recorded on Brucker Avance 500 MHz spectrometers using $CDCl_3$ as solvent and TMS as internal reference unless stated otherwise. Chemical shift value is expressed in δ ppm. Assignment of the protons and carbons in the carbohydrate ring was carried out using 1D ^1H, ^{13}C and ^{13}C DEPT NMR spectra and 2D COSY, HSQC NMR spectra. ESI-MS were recorded on a Micromass mass spectrometer. Commercially available grades of organic solvents of adequate purity are used in all reactions.

4.2. General experimental condition for the preparation of glycosyl thiourea derivatives

To a solution of glycosyl azide (1.0 mmol) and aryl isothiocyanate (1.2 mmol) in dry CH_3CN (5 mL) were added sulfamic acid (100 mg, 3.0 mmol) and sodium iodide (600 mg, 4.0 mmol) and the reaction mixture was allowed to stir at room temperature for appropriate time mentioned in Table 1. The solvents were removed under reduced pressure and the crude reaction mixture was diluted with CH_2Cl_2 (50 mL). The organic layer was successively washed with 5% $Na_2S_2O_3$ (50 mL), water (50 mL), dried (Na_2SO_4) and concentrated. The crude product was purified over SiO_2 column chromatography using hexane-EtOAc to give pure products. Spectral data of the isolated products, which are not reported earlier, are presented below.

***N*-(2,3,4,6-Tetra-O-acetyl-β-D-glucopyranosyl)-*N′*-(2,3-dichlorophenyl)thiourea (8):** Yellow oil; $[\alpha]_D^{25}$ – 6 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 7.52 (br s,1 H, N*H*), 7.47 - 7.30 (m, 3 H, Ar-H), 6.78 (d, *J* = 7.5 Hz, 1 H, N*H*), 5.68 (t, *J* = 8.5 Hz, 1 H, H-1), 5.33 (t, *J* = 9.5 Hz, 1 H, H-3) 5.02 (t, *J* = 10.0 Hz, 1 H, H-4), 4.88 (t, *J* = 9.5 Hz, 1 H, H-2), 4.34 (dd, *J* = 12.0 Hz, 5.5 Hz, 1 H, H-6_a), 4.08 (d, *J* = 12.0 Hz,1 H, H-6_b), 3.87 - 3.80 (m, 1 H, H-5), 2.06, 2.05, 2.03,

2.00 (4 s, 12 H, 4 C*H*$_3$CO); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 182.5 (*C*S), 171.3, 170.4, 169.6, 169.4 (4 C, 4 CH$_3$*C*O), 134.9 - 126.6 (6 C, Ar-C), 83.1 (C-1), 73.7 (C-5), 72.6 (C-3), 70.6 (C-2), 68.3 (C-4), 61.6 (C-6), 20.7, 20.6, 20.5, 20.4 (4 C,4 *C*H$_3$CO). ESI-MS: 573.0 $[M+Na]^+$; Anal. Calcd. for $C_{21}H_{24}Cl_2N_2O_9S$ (550.06): C, 45.74; H, 4.39%; found: C, 45.60; H, 4.56%.

***N*-(2,3,4,6-Tetra-O-acetyl-β-D-mannopyranosyl)-*N′*-(2,3-Dichlorophenyl)thiourea (14):** Yellow oil; $[\alpha]_D^{25}$ – 14 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.40 (br s, 1 H, N*H*), 7.66 - 7.22 (m, 3 H, Ar-H), 7.17 (d, *J* = 7.5 Hz, 1 H, N*H*), 5.87 (br s, 1 H, H-1), 5.38 (br s, 1 H, H-2), 5.09 - 5.04 (m, 2 H, H-3, H-4), 4.23 - 4.21 (m, 1 H, H-6$_a$), 3.98 (d, *J* = 12.5 Hz, 4.5 Hz, 1 H, H-6$_b$), 3.60 - 3.57 (m, 1 H, H-5), 2.06, 1.98, 1.97, 1.94 (4 s, 12 H, 4 CH$_3$CO); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 181.7 (*C*S), 170.4, 170.0, 169.4, 169.3 (4 CH$_3$*C*O), 133.4 - 127.4 (6 C, Ar-C), 80.8 (C-1), 74.0 (C-2), 71.4 (C-3), 69.8 (C-4), 65.4 (C-5), 62.2 (C-6), 20.9, 20.7, 20.5, 20.4 (4 *C*H$_3$CO). ESI-MS: 573.0 $[M+Na]^+$; Anal. Calcd. for $C_{21}H_{24}Cl_2N_2O_9S$ (550.06): C, 45.74; H, 4.39%; found: C, 45.57; H, 4.60%.

***N*-(2,3,4-Tri-O-acetyl-α-L-rhamnopyranosyl)-*N′*-(4-trifluoromethylphenyl)thiourea (15):** Yellow oil; $[\alpha]_D^{25}$ + 26 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.86 (br s, 1 H, N*H*), 7.63 - 7.45 (m, 4 H, Ar-H), 6.79 (br s, 1 H, N*H*), 5.94 (d, *J* = 9.0 Hz, 1 H, H-1), 5.42 (br s, 1 H, H-2), 5.07 (dd, *J* = 10.0 Hz, 3.0 Hz, 1 H, H-3), 4.91 (t, *J* = 10.0 Hz, 1 H, H-4), 3.70 - 3.64 (m, 1 H, H-5), 2.14, 2.03, 1.97, (3 s, 9 H, 3 C*H*$_3$CO), 1.18 (d, *J* = 6.5 Hz, 3 H, C*C*H$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 180.7 (*C*S), 170.0, 169.4, 169.3 (3 CH$_3$*C*O), 126.7 - 124.4 (6 C, Ar-C), 80.4 (C-1), 72.2 (C-3), 71.0 (C-4), 70.4 (C-2), 70.1 (C-5), 20.8, 20.6, 20.4, (3 *C*H$_3$CO), 17.4 (C*C*H$_3$). ESI-MS: 515.1 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{23}F_3N_2O_7S$ (492.12): C, 48.78; H, 4.71%; found: C, 48.60; H, 4.86%.

***N*-(2,3,4-Tri-O-acetyl-α-L-rhamnopyranosyl)-*N′*-(2,4-dichlorophenyl)thiourea (16):** Yellow oil; $[\alpha]_D^{25}$ – 9 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.32 (br s, 1 H, N*H*), 7.64 - 7.24

(m, 3 H, Ar-H), 6.90 (br s, 1 H, N*H*), 5.80 (br s, 1 H, H-1), 5.4 (br s, 1 H, H-2), 5.04 (dd, *J* = 10.0 Hz, 2.0 Hz, 1 H, H-3), 4.91(t, *J* = 10.0 Hz, 1 H, H-4), 3.68 - 3.64 (m, 1 H, H-5), 2.10, 2.02, 1.94 (3 s, 9 H, 3 CH_3CO), 1.18 (d, *J* = 5.5 Hz, 3 H, CCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 181.4 (*C*S), 170.0, 169.4, 169.3 (3 CH_3CO), 133.0 - 127.7 (6 C, Ar-C), 80.7 (C-1), 72.2 (C-3), 71.3 (C-4), 70.2 (C-2), 70.0 (C-5), 20.8, 20.7, 20.4 (3 CH_3CO), 17.4 (CCH_3). ESI-MS: 515.0 $[M+Na]^+$; Anal. Calcd. for $C_{19}H_{22}Cl_2N_2O_7S$ (492.05): C, 46.26; H, 4.49%; found: C, 46.10; H, 4.66%.

***N*-(2,3,4-Tri-O-acetyl-α-L-rhamnopyranosyl)-*N′*-(4-methylphenyl)thiourea (17):** Yellow oil; $[\alpha]_D^{25}$ – 3 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.25 (br s, 1 H, N*H*), 7.21 - 7.09 (m, 4 H, Ar-H), 6.37 (br s, 1 H, N*H*), 5.95 (d, *J* = 9.5 Hz, 1 H, H-1), 5.37 (br s, 1 H, H-2), 5.07 (dd, *J* = 10.0 Hz, 3.0 Hz, 1 H, H-3), 4.91 (t, *J* = 10.0 Hz, 1 H, H-4), 3.68 - 3.63 (m, 1 H, H-5), 2.38 (s, 3 H, Ar-CH_3), 2.15, 2.04, 1.95 (3 s, 9 H, 3 CH_3CO), 1.2 (d, *J* = 5.5 Hz, 3 H, CCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 180.8 (*C*S), 169.2 - 169.1 (3 CH_3CO), 138.9 - 125.7 (6 C, Ar-C), 80.5 (C-1), 72.0 (C-3), 71.1 (C-4), 70.0 (C-2, C-5), 20.6, 20.4, 20.3 (3 CH_3CO), 17.5 (CCH_3), 14.2 (Ar-CH_3). ESI-MS: 461.1 $[M+Na]^+$; Anal. Calcd. for $C_{20}H_{26}N_2O_7S$ (438.14): C, 54.78; H, 5.98%; found: C, 54.60; H, 6.20%.

***N*-(2,3,4-Tri-O-acetyl-α-L-rhamnopyranosyl)-*N′*-(2,3-dichlorophenyl)thiourea (18):** $[\alpha]_D^{25}$ – 7.6 (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 500 MHz): δ 8.37 (br s, 1 H, N*H*), 7.61 - 7.35 (m, 3 H, Ar-H), 6.94 (br s, 1 H, N*H*), 5.87 (br s, 1 H, H-1), 5.44 (br s, 1 H, H-2) 5.08 (dd, *J* = 10.0 Hz, 3.0 Hz, 1 H, H-3), 4.93 (t, *J* = 10.0 Hz, 1 H, H-4), 3.69 - 3.66 (m, 1 H, H-5), 2.11, 2.04, 1.96 (3 s, 9 H, 3 CH_3CO), 1.22 (d, *J* = 5.5 Hz, 3 H, CCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 181.2 (*C*S), 170.0, 169.4, 169.3 (3 CH_3CO), 136.0 - 125.4 (6 C, Ar-C), 80.7 (C-1), 72.2 (C-3), 71.3 (C-4), 70.2 (C-2), 70.0 (C-5), 20.8, 20.7, 20.5 (3 CH_3CO), 17.4 (CCH_3). ESI-MS: 515.0 $[M+Na]^+$; Anal. Calcd. for $C_{19}H_{22}Cl_2N_2O_7S$ (492.05): C, 46.26; H, 4.49%; found: C, 46.10; H, 4.66%.

***N*-(2,3,4-Tri-O-acetyl-α-L-rhamnopyranosyl-*N′*-(4-nitrophenyl)thiourea (19):** $[\alpha]_D^{25}$ + 6.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 9.09 (br s, 1 H, N*H*), 8.10 - 7.58 (m, 4 H, Ar-H), 7.23 - 7.21 (m, 1 H, N*H*), 5.93(d, *J* = 8.5 Hz, 1 H, H-1), 5.45 (d, *J* = 2.5 Hz, 1 H, H-2), 5.06 (dd, *J* = 10.0 Hz, 3.0 Hz, 1 H, H-3), 4.96 (t, *J* = 10.0 Hz, 1 H, H-4), 3.71 - 3.66 (m, 1 H, H-5), 2.16, 2.06, 1.97 (3 s, 9 H, 3 C*H*$_3$CO), 1.22 (d, *J* = 5.5 Hz, 3 H, CC*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 180.5 (*C*S), 170.4, 169.8, 169.5 (3 CH$_3$*C*O), 144.2 - 122.6 (6 C, Ar-C), 80.2 (C-1), 72.3 (C-3), 71.5 (C-4), 70.1 (C-2), 70.0 (C-5), 20.8, 20.7, 20.5, (3 *C*H$_3$CO), 17.5 (C*C*H$_3$). ESI-MS: 492.1 $[M+Na]^+$; Anal. Calcd. for $C_{19}H_{23}N_3O_9S$ (469.12): C, 48.61; H, 4.94%; found: C, 48.45; H, 5.10%.

***N*-(2,3,4-Tri-O-acetyl-α-L-rhamnopyranosyl)-*N′*-(4-fluorophenyl)thiourea (20):** Yellow oil; $[\alpha]_D^{25}$ – 12 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.54 (br s, 1 H, N*H*), 7.30 - 7.05 (m, 4 H, Ar-H), 6.46 (br s, 1 H, N*H*), 5.93 (d, *J* = 9.0 Hz, 1 H, H-1), 5.37 (d, *J* = 2.5 Hz, 1 H, H-2), 5.06 (dd, *J* = 10.0 Hz, 3.5 Hz, 1 H, H-3), 4.88 (t, *J* = 10.0 Hz, 1 H, H-4), 3.70 - 3.60 (m, 1 H, H-5), 2.02, 1.98, 1.95, (3 s, 9 H, 3 C*H*$_3$CO), 1.18 (d, *J* = 6.0 Hz, 3 H, CC*H*$_3$); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 181.0 (*C*S), 169.6, 169.3, 169.2 (3 CH$_3$*C*O), 132.0 - 116.7 (6 C, Ar-C), 80.5 (C-1), 72.1 (C-3), 71.2 (C-4), 70.1 (C-2), 70.0 (C-5), 20.6, 20.5, 20.4 (3 *C*H$_3$CO), 17.4 (C*C*H$_3$). ESI-MS: 465.1 $[M+Na]^+$; Anal. Calcd. for $C_{19}H_{23}FN_2O_7S$ (442.12): C, 51.58; H, 5.24%; found: C, 51.40; H, 5.40%.

***N*-[2,3,4,6-Tetra-O-acetyl-β-D-galactopyranosyl)-(1→4)-2,3,6-tri-O-acetyl-β-D-glucopyranosyl]-*N′*-(4-nitrophenyl)thiourea (21)**: Yellow oil; $[\alpha]_D^{25}$ + 6 (*c* 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.90 (br s, 1 H, N*H*), 7.95 (d, *J* = 9.0 Hz, 2 H, Ar-H), 7.62 (d, *J* = 8.5 Hz, 2 H, Ar-H), 7.08 (s, 1 H, N*H*), 5.66 (t, *J* = 9.0 Hz, 1 H, H-1), 5.30-5.28 (m, 2 H, H-4$_B$, H-2$_A$), 5.11 (t, 1 H, H-3$_A$), 4.99 (dd, *J* = 3.0 Hz, 1 H, H-2$_B$), 4.71 (t, *J* = 11.0 Hz, 1 H, H-3$_B$), 4.56 (d, *J* = 7.5 Hz, 1 H, H-1$_B$), 4.18 - 4.10 (m, 4 H, H-6$_{abB}$, H-6$_{abA}$), 4.05 (t, *J* = 9.0 Hz, 1 H, H-

5_B), 3.88 (t, *J* = 5.5 Hz, 1 H, H-4_A), 3.80 (t, *J* = 8.5 Hz, 1 H, H-5_A), 2.18, 2.14, 2.11, 2.09, 2.07, 2.04, 2.03, (7 s, 21 H, 7 COCH_3); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 182.1 (*C*S), 170.6, 170.3 (2 C), 169.9, 169.7, 169.5, 169.4 (7 *C*OCH$_3$), 146.0, 143.1, 131.6, 130.0, 129.3, 126.8 (Ar-C), 100.1 (C-1_B), 81.1 (C-1_A), 76.4 (C-5_A), 73.8 (C-5_B), 73.4 (C-3_A), 71.0 (C-4_A), 70.8 (C-3_B), 70.1 (C-2_A), 69.2 (C-2_B), 67.5 (C-4_B), 62.7 (C-6_B), 61.3 (C-6_A), 22.5, 21.1, 20.9 (2 C), 20.8, 20.7 (2 C), (7 CO*C*H$_3$). ESI-MS: 838.2 $[M+Na]^+$; Anal. Calcd. for $C_{33}H_{41}N_3O_{19}S$ (815.21): C, 48.59; H, 5.07%; found: C, 48.45; H, 5.25%.

General method for the de-O-acetylation of glycosyl thiourea derivatives: A solution of per-*O*-acetylglycosyl thiourea derivative (100 mg) in 0.05 M CH_3ONa (5 mL) was allowed to stir at room temperature for 2 h. The reaction mixture was neutralized with Dowex X8 (H^+) resin, filtered and concentrated under reduced pressure. The crude product was passed through a short pad of SiO_2 using EtOAc as eluant to give pure de-O-acetylated products in quantitative yield.

***N*-(β-D-Glucopyranosyl-*N′*-(4-nitrophenyl)thiourea (10a):** glassy syrup; $[\alpha]_D^{25}$ + 5 (*c* 1.0, CH_3OH); ^{1}H NMR (D_2O, 500 MHz): δ 8.31 (d, *J* = 9.0 Hz, 2 H, Ar-H), 7.68 (d, *J* = 9.0 Hz, 2 H, Ar-H), 5.65-5.60 (br s, 1 H, H-1), 3.95-3.91 (dd, *J* = 12.0, 2.0 Hz, 1 H, H-6_a), 3.81-3.74 (dd, *J* = 12.0, 5.0 Hz, H-6_b), 3.64-3.58 (m, 2 H, H-2, H-5), 3.53 (t, *J* = 9.0 Hz, 1 H, H-3), 3.46 (t, *J* = 9.0 Hz, 1 H, H-4); ^{13}C NMR (D_2O, 125 MHz): δ 181.9 (*C*S), 146.3-121.3 (Ar-C), 83.8 (C-1), 78.8, 77.9, 72.9, 70.1, 63.1; ESI-MS: 382.0 $[M+Na]^+$; Anal. Calcd. for $C_{13}H_{17}N_3O_7S$ (359.08): C, 43.45; H, 4.77%; found: C, 43.25; H, 5.00%.

***N*-(β-D-Glucopyranosyl-*N′*-(2,3-dichlorophenyl)thiourea (12a):** glassy syrup; $[\alpha]_D^{25}$ − 8 (*c* 1.0, CH_3OH); ^{1}H NMR (D_2O, 500 MHz): δ 9.16 (br s, 1 H, NH), 8.46 (br s, 1 H, NH), 8.02-7.80 (m, 3 H, Ar-H), 5.82-5.78 (m, 1 H, H-1), 4.27-4.11 (m, 2 H, H-6_{ab}), 3.95-3.73 (m, 4 H, H-2, H-3, H-4, H-5); ^{13}C NMR (D_2O, 125 MHz): δ 183.8 (*C*S), 133.9-128.1 (Ar-C), 84.1 (C-1), 77.7,

76.8, 72.3, 69.7, 61.0; ESI-MS: 405.0 $[M+Na]^+$; Anal. Calcd. for $C_{13}H_{16}Cl_2N_2O_5S$ (382.02): C, 40.74; H, 4.21%; found: C, 42.53; H, 4.45%.

***N*-(α-L-Rhamnopyranosyl)-*N′*-(2,4-dichlorophenyl)thiourea (16a):** glassy syrup; $[\alpha]_D^{25}$ + 9 (*c* 1.0, CH_3OH); ^1H NMR (D_2O, 500 MHz): δ 8.03-7.80 (m, 3 H, Ar-H), 5.96 (br s, 1 H, H-1), 4.40 (br s, 1 H, H-2), 4.06 (dd, *J* = 9.5, 3.5 Hz, 1 H, H-3), 3.92-3.85 (m, 1 H, H-5), 3.77 (t, *J* = 10.5 Hz, 1 H, H-4), 1.69 (d, *J* = 6.5 Hz, 3 H, CC*H*$_3$); ^{13}C NMR (D_2O, 125 MHz): δ 182.6 (*C*S), 133.9-128.1 (Ar-C), 82.0 (C-1), 73.9, 73.4, 72.0, 70.1, 17.0 (C*C*H_3); ESI-MS: 389.0 $[M+Na]^+$; Anal. Calcd. for $C_{13}H_{16}Cl_2N_2O_4S$ (366.02): C, 42.52; H, 4.39%; found: C, 42.33; H, 4.60%.

Acknowledgements

A.G. and M.J. thank CSIR, New Delhi for providing Junior and senior research fellowships respectively. This work was supported by SERB, New Delhi (Project No. EMR/2015/000282).

Reference

1. Shakeel, A.; Altaf, A. A.; Qureshi, A. M.; Badshah, A. *J. Drug Design Med. Chem.* **2016**, *2*, 10-20.
2. Sudzhaev, A. R.; Rzaeva, I. A.; Nadzhafova, R. A.; Safarov, Y. S.; Allakhverdiev, M. A. *Russ. J. Appl. Chem*. **2011**, *84*, 1394-1397.
3. Venkatesh, P.; Pandeya, S. *Int. J. Chem Tech. Res*. **2009**, *1*, 733-741.
4. Sondhi, S.; Sharma, V. K.; Singhal, N.; Verma, R.; Shukla, R.; Raghubir, R.; Dubey, M. *Phosphorus, Sulfur, and Silicon Related Elements*. **2000**, *156*, 21-33.
5. Mahajan, A.; Yeh, S.; Nell, M.; van Rensburg, C. E. J.; Chibale, K. *Bioorg. Med. Chem. Lett*. **2007**, *17*, 5683-5685.
6. Buran, K.; Durmaz, I.; Cetin, R.; Onen-Bayram, F. E. *Med. Chem. Commun.* **2015**, *1*, 90-93.

7. Sriram, D.; Yogeeswari, P.; Dinakaran, M.; Irumurugan, R. *J. Antimicrob. Chemotherapy*, **2007**, *59*, 1194-1196.
8. Richter, C. P. *J. Am. Med. Asso*. **1945**, *129*, 927-931.
9. Huang, X. C.; Wang, M.; Pan, Y. M.; Yao, G. Y.; Wang, H. S.; Tian, X. Y.; Qin, J. K.; Zhang, Y. *Eur. J. Med. Chem*. **2013**, *69*, 508-520.
10. Wu, J.; Shi, Q.; Chen, Z.; He, M.; Jin, L.; Hu, D. *Molecules* **2012**, *17*, 5139-5150.
11. Tunaz, H.; Uygun, N. *Turk. J. Agric. Forest*. **2004**, *28*, 377-456.
12. Ke, S.-Y.; Xue, S.-J. *Arkivoc* **2006**, *10*, 63-68.
13. Kodomari, M.; Suzuki, M.; Tanigawa K.; Aoyama, T. *Tetrahedron Lett*, **2005**, *46*, 5841-5843.
14. Rambo, R. S.; Jacoby, C. G.; da Silva, T. L.; Schneider, P. H. *Tetrahedron: Asymmetry* **2015**, *26*, 632-637.
15. Zhang, Z.; Schreiner, P. R. *Chem. Soc. Rev*. **2009**, *38*, 1187-1198.
16. Jiang, X.; Shi, X.; Wang, S.; Sun, T.; Cao, Y.; Wang, R. *Angew. Chem. Int. Ed. Engl.* **2012**, *51*, 2084-2087.
17. Goffin, E.; Lamoral-Theys, D.; Tajeddine, N.; De Tullio, P.; Mondin, L.; Lefranc, F.; Gailly, P.; Rogister, B.; Kiss, R.; Pirotte, B. *Eur. J. Med. Chem*. **2012**, *54*, 834-844.
18. Abdolmaleki, A. *J. Appl. Polym. Sci*. **2012**, *124*, 2508-2512.
19. Fuentes, J.; Angulo, M.; Pradera, M. A. *J. Org. Chem*. **2002**, *67*, 2577-2587.
20. Todoulou, O. G.; Papadaki-Valiraki, A. E.; Filippatos, E. C.; Ikeda, S.; De Clercq, E. *Eur. J. Med. Chem*. **1994**, *29*, 127-131.
21. Fuentes, J.; Molina, J. L.; Pradera, M. A. *Tetrahedron: Asymm*. **1998**, *9*, 2517-2532.
22. Gasch, C.; Pradera, M. A.; Salameh, B. A. B.; Molina, J. L.; Fuentes, J. *Tetrahedron: Asymm*. **2001**, *12*, 1267-1277.
23. Dubber, M.; Lindhorst, T. K. *Org. Lett*. **2001**, *3*, 4019-4022.

24. Saitz-Barrie, C.; Torres-Pinedo, A.; Santoyo González, F. *Synlett* **1999**, 1891-1894.

25. García Fernández, J. M.; Ortiz Mellet, C. *Adv. Carbohydr. Chem. Biochem.* **2000**, *55*, 35-135.

26. McKay, M. J.; Nguyen, H. M. *Carbohydr. Res.* **2014**, *385*, 18-44.

27. Maya, I.; López, Ó.; Fernández-Bolaños, J. G.; Robina, I.; Fuentes, J. *Tetrahedron Lett.* **2001**, *42*, 5413-5416.

28. López, Ó.; Maya, I.; Fuentes, J.; Fernández-Bolaños, J. G. *Tetrahedron* **2004**, *60*, 61-72.

29. Kamal, A.; Shankaraiah, N.; Markandeya, N.; Reddy, C. S. *Synlett*, **2008**, 1297-1300.

30. Shankaraiah, N.; Kumar, N. P.; Amula, S. B.; Nekkanti, S.; Jeengar, M. K.; Naidu, V. G. M.; Reddy, S.; Kamal, A. *Bioorg. Med. Chem. Lett.* **2015**, *25*, 4239-4244.

31. Brahmachari, G.; Banerjee, B. *Curr. Organocatal.* **2016**, *3*, 93-124.

32. Somsák, L.; Felföldi, N.; Kónya, B.; Huse, C.; Telepo, K.; Bokor, É.; Czifrák, K *Carbohydr. Res.* **2008**, *343*, 2083-2093.

33. Wang, X. –M.; Zhu, T.; Zheng, L. –Y.; Li, Y. –X.; Zhang, S. –Q.; Bai, J. *Youji Huaxue* **2006**, *26*, 660-669.

34. Bognár, R.; Somogyi, L.; Szilágyi, L.; Györgydeák, Z. *Carbohydr. Res.* **1967**, *5*, 320-328.

35. Ali, A. U.; Meshram, H. M.; Paranjpe, M. G. *J. Ind. Chem. Soc.* **1985**, *62*, 666-669.

36. Hardas, A. R.; Ulhe, A. G.; Bhiwagade, S. M.; Berad, B. N. *Pharma Chemica* **2013**, *5*, 263-266.

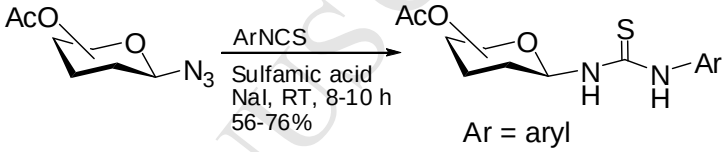
37. Dhonde, M. G.; Wankhade, A. V.; Deshmukh, S. P. *J. Chem. Pharm. Res.* **2010**, *2*, 518-525.

38. Kumar, R.; Tiwari, P.; Maulik, P. R.; Misra, A. K. *Eur. J. Org. Chem.* **2005**, 74-79.

Graphical abstract

Preparation of glycosyl thiourea derivatives from glycosyl azides using sulfamic acid and sodium iodide in one-pot

Arin Gucchait, Manas Jana, Kuladip Jana and Anup Kumar Misra*



Research Highlights

- Glycosyl thiourea derivatives were prepared directly from glycosyl azides.
- Sulfamic acid and sodium iodide has been used for the reduction of azide group.
- Non-metallic and non-hazardous reaction condition.
- Aryl isothiocyanates reacted with *in situ* generated glycosyl amine derivatives.