

SYNTHESIS OF NOVEL SUBSTITUTED BENZALDEHYDE (HEPTA-O-ACETYL- β -LACTOSYL)THIOSEMICARBAZONES

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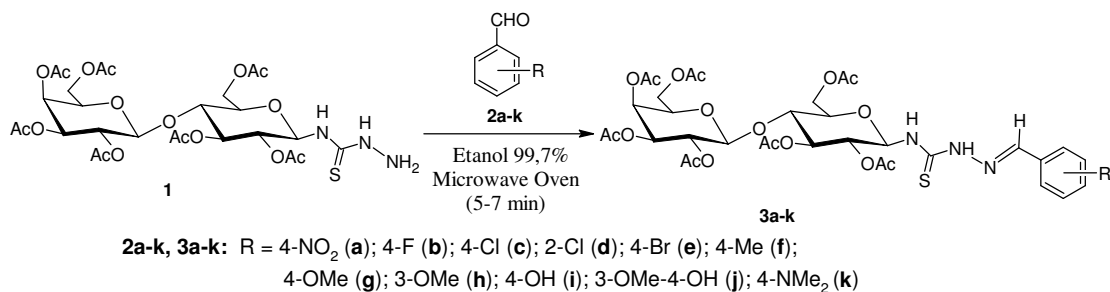
ABSTRACT

A series of substituted benzaldehyde hepta-O-acetyl- β -lactosyl thiosemicarbazones were synthesized by condensation reactions of hepta-O-acetyl- β -lactosyl thiosemicarbazide with corresponding substituted benzaldehydes. Structures of thiosemicarbazones were confirmed by spectroscopic (IR, NMR) methods.

Thiosemicarbazones are a class of small molecules that have been evaluated over the last 50 years as antivirals and as anticancer therapeutics, as well as for their parasitocidal action against *Plasmodium falciparum* and *Trypanosoma cruzi* which are the causative agents of malaria and Chagas's disease, respectively. The chemistry of thiosemicarbazide derivatives of saccharides is interested [1]. These compounds arouse interest as versatile intermediates for preparing various (e.g., heterocyclic) derivatives as well.

Thiosemicarbazones can be used for making electrodes [2], or complexes formation of metallic ions [3]. Thiosemicarbazones exhibit various biological activities such as antituberculosis, antimicrobial, anti-inflammatory, antiviral, anticonvulsant [4].

Continuing the previous papers [5], we now report here for the first time the synthesis and characterization of hepta-O-acetyl- β -lactosyl thiosemicarbazide from peracetylated lactosyl isothiocyanate and its reaction with a series of aromatic aldehydes as shown in scheme 1.



Scheme 1

Hepta-O-acetyl- β -lactosyl thiosemicarbazide (**1**) was synthesized by condensation of hepta-O-acetyl- β -lactosyl isothiocyanate and hydrazine hydrate in

absolute dioxane at 15 - 20°C. The IR spectrum shows the characteristic stretching vibrations for the NH and NH₂ groups in the thiosemicarbazide group (-NH-C(=S)-NH-

NH₂) at 3337, 3290 and 3202 cm⁻¹, for the ester at 1746, 1234 and 1044 cm⁻¹, and for the C=S bond at 1370 cm⁻¹. The ¹H-NMR spectrum of hepta-*O*-acetyl-β-lactosyl thiosemicarbazide contains chemical shifts characteristic of the peracetated-β-lactosyl thiosemicarbazide. For example, the chemical shifts of the NH and NH₂ groups are observed at 9.23 ppm (NH), 8.12 ppm (NH), and 4.58 ppm (N-H_c), while those of the disaccharide component are observed at 5.78-3.91 ppm. The anomeric configuration of the pyranose rings in this thiosemicarbazide is clearly established by ¹H-NMR spectroscopy. The β anomeric D-glucose moiety shows a characteristic signal for H-1 (*J*_{1,2} = 10.0 Hz), which is consistent with the 1,2-trans relationships between protons. The α anomeric D-glucose moiety shows a characteristic signal for H-1' (*J*_{1',2'} = 4.0 Hz), which is consistent with the 1,2-cis relationships between protons. The ¹³C-NMR spectrum shows resonance signals at 95.34 - 61.43 ppm for the lactosyl carbons, 170.16-169.21 ppm for the seven C=O groups in the esters, 20.63 - 20.27 ppm for the methyl carbons of acetyl groups and 182.11 ppm for the C=S group.

The new substituted benzaldehyde (hepta-*O*-acetyl-β-lactosyl)thiosemicarbazones (**3a-k**) were obtained by condensation of hepta-*O*-acetyl-β-lactosyl thiosemicarbazide (**1**) with the corresponding substituted benzaldehydes (**2a-k**) in 70 - 87% yields (table 1). Reactions are performed in absolute ethanol in the presence of glacial acetic acid as a catalyst by microwave-assisted method. The IR spectra show characteristic absorptions in the range of 3540 - 3480 cm⁻¹ (ν_{OH}) and 3348 - 3159 cm⁻¹ (ν_{NH}), 1737 - 1753 (ν_{C=O} ester), 1216 - 1252 and 1044 - 1056 cm⁻¹ (ν_{COC} ester), 1367 - 1377 cm⁻¹ (ν_{C=S}), and 1580 - 1615 cm⁻¹ (ν_{CH=N}). The ¹H-NMR spectrum of hepta-*O*-acetyl-β-lactosyl thiosemicarbazones (**3a-k**) shows chemical shifts at δ 11.67 - 12.16 ppm (NH-1) in singlet, δ 8.41 - 8.88 ppm (NH-3) in doublet with coupling constants *J* = 9.0 - 9.5 Hz, δ 7.97 - 8.18 ppm (CH=N) in singlet. The aromatic

protons have signals at δ 6.72 - 8.25 ppm with the coupling constants *J* which appropriate to substituted benzene ring (Table 2). The protons in lactose moiety have chemical shifts in region δ 4.00 - 6.00 ppm. The β anomeric configuration of **3a-k** is confirmed on the basis of the coupling constant *J*_{1,2} = 9.0 Hz, which is consistent with a 1,2-trans relationships between protons (Table 3). The ¹³C-NMR spectrum of compound **3a-k** shows signals at δ 179.1 - 177.3 ppm for the carbon atom in the C=S group, δ 170.7 - 169.0 ppm for the carbon atoms in the C=O bond of the acetyl groups, δ 111.0 - 150.0 ppm for the carbon atoms in benzene ring and 20.7-20.1 ppm for the methyl carbons in the acetyl groups; the carbon atom in imine group CH=N show signals at δ 140.2 - 147.8 ppm (table 4).

III - EXPERIMENTAL

Melting points were determined on a STUART SMP3 apparatus (BIBBY STERILIN-UK). The FTIR-spectra were recorded on a Magna 760 FT-IR Spectrometer (NICOLET, USA) in KBr pellets. The ¹H-NMR (500.13 MHz), ¹³C-NMR (125.77 MHz) spectra were recorded on an AVANCE AV500 Spectrometer (BRUKER, Germany) in DMSO-*d*₆ solution in ppm compared to TMS as internal reference at 300K.

General synthetic method of substituted benzaldehyde (hepta-*O*-acetyl-β-lactosyl)-thiosemicarbazones (3a-k**).** A mixture of hepta-*O*-acetyl-β-maltosyl thiosemicarbazide **1** (1 mmol), benzaldehyde **2** (1 mmol), glacial acetic acid (0.5 ml) in absolute ethanol (in the presence of glacial acetic acid as catalyst) or glacial acetic acid (20 ml) was heated at reflux using domestic microwave oven TIFANY 750W in 5-7 min. The solvent was evaporated to one half the original volumes. The resulting colorless crystals were filtered by suction. The crude product when recrystallized from 96% ethanol to afford the title compounds **3**.

Table 1: Substituted benzaldehyde (hepta-*O*-acetyl- β -lactosyl)thiosemicarbazones **3a-k**

Entry	R	mp, °C	Yield, %	IR spectra, cm ⁻¹				
				ν_{NH}	$\nu_{\text{CH=N}}$	$\nu_{\text{C=O ester}}$	$\nu_{\text{COC ester}}$	$\nu_{\text{C=S}}$
3a	4-NO ₂	172-173	87	3325	1580	1746	1231,1056	1376
3b	4-F	159-160	70	3320	1601	1752	1238,1048	1376
3c	4-Cl	189-190	76	3279, 3215	1605	1751	1222,1046	1371
3d	2-Cl	187-188	78	3309	1615	1750	1216,1052	1375
3e	4-Br	155-156	78	3334	1605	1749	1231,1064	1367
3f	4-Me	177-178	78	3212	1615	1748	1242,1046	1373
3g	4-OMe	198-199	76	3348, 3284	1604	1737	1252, 1228,1044	1370
3h	3-OMe	196-197	73	3344, 3159	1605	1747	1241,1042	1376
3i	4-OH	161-162	78	3548*, 3340, 3275	1609		1238,1042	1372
3j	3-OMe- 4-OH	176-177	76	3480*, 3337	1603	1749	1224,1051	1377
3k	4-NMe ₂	187-188	77	3320	1604	1753	1252, 1220,1054	1372

Note: *) also ν_{OH} .

Table 2: ¹H NMR spectral data of compounds 3a-k in aromatic moiety (δ in ppm, multiplicity, J in Hz)

Proton	NH-1	NH-3	CH=N	H-2'''	H-3'''	H-4'''	H-5'''	H-6'''
3a	12.16,s	8.88,d,9.0	8.18,s	8.10,d,9.0	8.25,d,9.0	-	8.25,d,9.0	8.10,d,9.0
3b	11.90,s	8.66,d,9.0	8.09,s	7.88,d,5.5, 8.5	8.10,d,8.5	-	8.10,d,8.5	7.88,d,5.5, 8.5
3c	11.95,s	8.70,d,9.0	8.08,s	7.85,d,8.5	7.49,d,8.5	-	7.49,d,8.5	7.85,d,8.5
3d	12.08,s	8.75,d,9.0	8.52,s	-	7.51,dd,0.5, 8.0	7.44,td,2.0, 7.25''	7.40,t,7.25''	8.27,dd,1.5, 7.5
3e	12.00,s	8.70,d,9.0	8.08,s	7.82,d,8.5	7.66,d,8.5	-	7.66,d,8.5	7.82,d,8.5
3f	11.86,s	8.59,d,9.5	8.06,s	7.69,d,8.5	7.25,d,8.5	-	7.25,d,8.5	7.69,d,8.5
3g	11.81,s	8.55,d,9.0	8.05,s	7.75,d,8.5	6.99,d,8.5	-	6.99,d,8.5	7.75,d,8.5
3h	11.95,s	8.62,d,9.0	8.07,s	7.44,s	-	7.00,dd,1.5, 8.0''	7.34,t,8.0''	7.31,t,8.0
3i	11.76,s	8.51,d,9.5	8.00,s	6.81,d,8.5	7.64,d,8.5	-	7.64,d,8.5	6.81,d,8.5
3j	11.84,s	8.50,d,9.0	7.98,s	7.46,d,1.5	-	-	6.81,d,8.0''	7.10,dd,1.5, 8.25
3k	11.67,s	8.41,d,9.5	7.97,s	7.59,d,8.5	6.72,d,8.5	-	6.72,d,8.5	7.59,d,8.5

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Table 3: ¹H NMR spectral data of compounds **3a-k** in lactose moiety (δ in ppm, multiplicity, J in Hz)

R	4-NO ₂	4-F	4-Cl	2-Cl	4-Br	4-Me-	4-OMe-	3-OMe	4-OH	3-OMe-4-OH	4-NMe ₂
Proton	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k
H-1'	5.88,t,9.0	5.85,t,9.25	5.85,t,9.0	5.86,t,9.0	5.90,t,9.0	5.84,t,9.0	5.83,t,9.25	5.79,t,9.0	5.83,t,9.25	5.74,t,9.25	5.82,t,9.0
H-2'	5.24–5.21,m	5.19,1H, 9.25	5.20,t,9.25	5.23,t,9.25	5.24,t,9.25	5.19,t,9.5	5.18,t,9.25	5.18,t,9.25	5.18,t,9.25	5.17–5.13, m	5.17– 5.14,m,
H-3'	5.31,t,9.25	5.30,d,9.25	5.30,t,9.25	5.30,t,9.25	5.33,t,9.25	5.30,t,9.25	5.30,t,9.0	5.31,t,9.25	5.30,t,9.25	5.33,t,9.25	5.30,t,9.0
H-4'	3.81,t,9.25	3.81,t,9.5	3.80,t,9.5	3.80,t,9.5	3.84,t,9.75	3.81,t,9.5	3.82–3.79,m	3.81,t,9.0	3.80,t,9.75	3.85–3.81,m	3.81,t,9.25
H-5'	3.90–3.87,m	3.90–3.87,m	3.90–3.88,m	3.90–3.88,m	3.94–3.91,m	3.90–3.87,m	3.89–3.87,m	3.88,ddd,3.5 , 5.5, 10.0	3.89–3.86,m	3.85–3.81,m	3.88–3.85,m
H-6'a	4.31,d,11.5	4.31,d,11.5	4.30,d,11.5	4.33–4.30,m	4.33,d,11.0	4.30,d,11.0	4.30,d,11.5	4.30,d,11.0	4.30,d,11.0	4.29,d,11.0	4.30,d,11.0
H-6'b	4.07,dd,5.5, 12.5	4.07,dd,5.5, 11.0	4.08– 4.05,mb	4.06,dd,5.25, 12.25	4.09,dd,5.5, 12.0	4.07,dd,5.75 , 12.25	4.09–4.05,m	4.07,dd,6.75 , 12.5	4.06,dd,5.5, 9.5	4.07,dd,5.5, 12.0b	4.09–4.05,m
H-1''	4.80,d,8.0	4.80,d,8.0	4.80,d,7.5	4.80,d,8.0	4.83,d,8.0	4.80,d,8.0	4.80,d,7.5	4.79,d,7.5	4.80,d,8.0	4.78,d,8.0	4.79,d,7.5
H-2''	4.88,t,8.75	4.88,dd,3.25 , 10.5	4.88,t,9.0	4.87,dd,3.0, 10.0	4.91,dd,3.0, 11.5	4.88,t,9.0	4.88,t,9.25	4.88,dd,3.0, 10.0	4.87,dd,3.0, 10.0	4.87,dd,3.0, 10.0	4.88,t,9.0
H-3''	5.15,dd,3.5, 10.0	5.17,dd,3.75 , 9.75	5.16,dd,10.0 , 3.5	5.15,dd,3.5, 10.0	5.16,dd,3.75 , 10.25	5.15,dd,10.5 , 3.5	5.15,dd,3.0, 10.0	5.15,dd,10.5 , 3.5	5.16,dd,4.0, 10.0	5.17–5.13,m	5.17–5.14,m
H-4''	5.24–5.21,m	5.24,d,3.5	5.24,d,3.5	5.24,d,3.0	5.28,d,3.5	5.24,d,3.5	5.24,d,3.0	5.24,d,3.5	5.24,d,3.5	5.24,d,3.5	5.25,d,2.5
H-5''	4.25,t,6.5	4.25,t,6.5	4.25,t,6.0	4.25,t,6.75	4.29,t,6.5	4.25,t,6.5	4.24,t,6.75	4.24,t,6.75	4.25,t,6.75	4.25,t,6.75	4.25,t,6.0
H-6''a & H-6''b	4.03,d,6.0	4.04–4.02,m	4.04–4.03,m	4.03–4.02,m	4.07–4.05,m	4.04–4.03,m	4.04–4.03,m	4.03,d,6.5	4.03–4.02,m	4.04–4.02,m	4.04–4.03,m
COCH ₃	2.11-2.01	2.11-2.01	2.11–1.91	2.11–1.92	2.15–1.94	2.11–1.90	2.11–1.91	2.11–2.01	2.11–1.90	2.11–1.91	2.11–1.91
Other proton						2.34,s, 3H, 4'''-CH ₃	3.81,s, 3H, 4'''-OCH ₃	3.83,s, 3H, 3'''-OCH ₃	9.97,s,4'''- OH	9.57,s,4'''- OH	2.97 [s, 6H, 4'''- N(CH ₃) ₂],
Other proton										3.86,3'''- OCH ₃)	

Table 4. ¹³C NMR spectral data of compounds **3a-k** (δ in ppm)

R	4-NO ₂	4-F	4-Cl	2-Cl	4-Br	4-Me-	4-OMe-	3-OMe	4-OH	3-OMe-4- OH	4-NMe ₂
Carbon	3a	3b	3c	3d	3e	3f	3g	3h	3i	3j	3k
C=S	178.8	178.4	178.3	179.1	178.4	178.2	177.8	178.4	177.7	177.8	177.3
COCH₃	170.2– 169.0	170.2– 169.1	170.5– 169.4	170.7– 169.5	170.2– 169.0	170.2– 169.0	170.5– 169.4	170.2– 169.0	170.2– 169.0	170.2– 169.0	170.2– 169.0
CH=N	141.1	142.6	142.7	140.2	142.5	143.9	144.1	143.5	144.1	144.1	144.8
C-1'''	140.2	130.4	132.5	133.9	133.0	131.0	126.0	135.1	124.6	125.1	120.8
C-2'''	128.4	129.7	129.8	132.1	129.4	127.5	129.2	111.4	129.4	109.5	128.9
C-3'''	123.8	115.7	128.8	130.3	131.7	129.3	114.2	159.6	115.6	148.1	111.6
C-4'''	147.8	163.3	134.9	131.6	123.5	140.2	161.1	116.5	159.6	149.6	151.7
C-5'''	123.8	115.7	128.8	127.8	131.7	129.3	114.2	129.6	115.6	115.3	111.6
C-6'''	128.4	129.7	129.8	128.0	129.4	127.5	129.2	120.7	129.4	122.6	128.9
C-1'	81.3	81.3	81.2	81.7	81.2	81.2	81.1	81.2	81.1	81.0	81.1
C-2'	71.2	71.1	70.9	71.6	71.1	71.1	70.9	70.9	71.1	70.8	71.0
C-3'	72.8	72.7	72.6	73.2	72.7	72.7	72.6	72.5	72.7	72.4	72.7
C-4'	76.0	76.0	75.9	76.5	76.0	76.0	75.9	76.1	76.1	76.2	76.1
C-5'	73.4	73.4	73.5	73.9	73.4	73.4	73.5	73.4	73.3	73.3	73.4
C-6'	62.4	62.4	62.2	62.8	62.4	62.3	62.2	62.3	62.3	62.3	62.3
C-1''	99.6	99.6	99.6	100.1	99.6	99.6	99.6	99.6	99.6	99.6	99.6
C-2''	68.9	68.9	68.8	69.3	68.8	68.9	68.8	68.8	68.8	68.8	68.9
C-3''	70.4	70.4	70.3	70.9	70.4	70.4	70.3	70.4	70.3	70.4	70.4
C-4''	67.1	67.1	67.0	67.6	67.1	67.1	67.1	67.1	67.1	67.1	67.1
C-5''	69.7	69.8	69.7	70.2	69.7	69.7	69.7	69.7	69.7	69.7	69.7
C-6''	61.0	61.0	60.9	61.5	60.9	60.9	60.9	60.9	60.9	60.9	60.9
COCH₃	20.7– 20.3	20.7– 20.2	20.5– 20.1	21.2– 20.8	20.7– 20.4	20.6– 20.2	20.5– 20.1	20.6– 20.2	20.7– 20.3	20.7– 20.3	20.6– 20.2
						21.0 (4'''-CH ₃)	55.2 (4'''-OCH ₃)	55.2 (3'''- OCH ₃)		55.7 (3'''-OCH ₃)	40.0 [4'''- N(CH ₃) ₂]
Other C											