SOME CONVERSIONS OF PER-*O*-ACETYL-β-D-GLYCOPYRANOSYL THIOSEMICARBAZONES OF SUBSTITUTED ACETOPHENONES AND BENZALDEHYDES

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Abstract–Some novel substituted acetophenone and benzaldehyde (2',3',4',6'-tetra-*O*-acetyl-β-D-glycopyranosyl)thiosemicarbazones **5** and **6** were synthesized by reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glycopyranosyl thiosemicarbazide **3** and **4** and substituted acetophenones anfd belzandehydes. The compounds **5** and **6** have been converted into 2-iminothiazolidin-4-ones **7**/7' and **8/8'** by reaction with ethyl bromoacetate in dichloromethane in the presence of anhydrous sodium acetate. Structures of obtained compounds were confirmed by spectroscopic methods.

1. Introduction

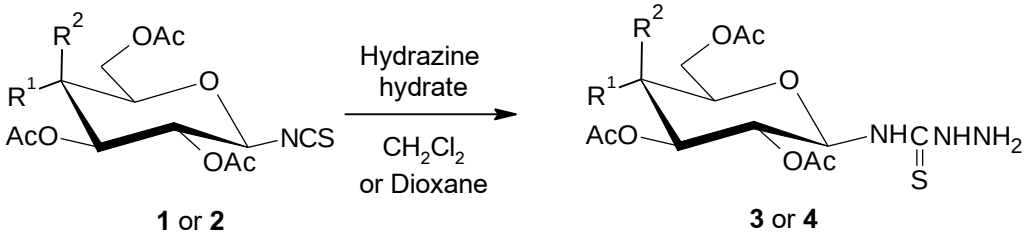
Thiosemicarbazones are a class of small molecules that have been evaluated over the last 50 years as antivirals and as anticancer therapeutics, as well as for their parasiticidal action against *Plasmodium falciparum* and *Trypanasoma cruzi* which are the causative agents of malaria and Chagas's disease, respectively [1]. The chemistry of thiosemicarbazide derivatives of saccharides is interested [2]. These compounds arouse interest as versatile intermediates for preparing various (e.g., heterocyclic) derivatives as well. Thiosemicarbazones can be used for making electrodes, or complexes formation of metallic ions [3]. Thiosemicarbazones exhibit various biological activities such as antituberculosis, antimicrobial, anti-inflammatory, antiviral, anticonvulsant, antihypertensive, local anesthetic, anticancer, hypoglycemic and cytotoxic activities [4]. In the past, some papers have been published for the synthesis of aldehyde/ketone per-*O*-acetylated glycopyranosyl thiosemicarbazones [5]. The main synthetic step for the synthesis of these molecules is being the reaction of a glycosyl thiosemicarbazide with a carbonyl compound. Continuing our studied on the synthesis and the reactivity of peracetated glycopyranosyl isothiocyanate and thiosemicarbazides [5,6], we report herein a systematic study for the synthesis and spectral characterization of a series of aromatic ketone 4-(β-D-glucopyranosyl)-thiosemicarbazones using microwave-assisted method [5d].

3. Results and discussion

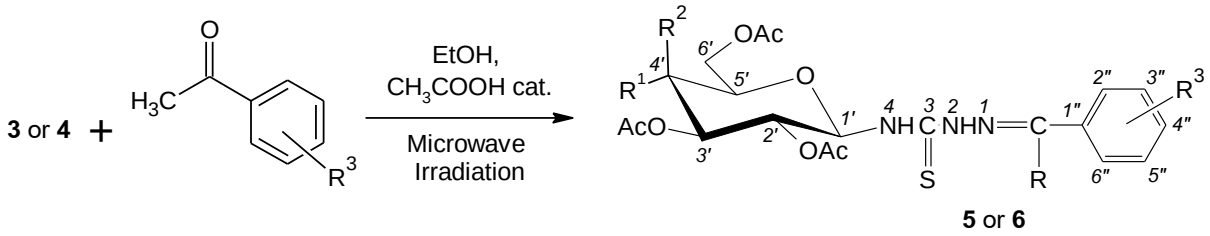
The required peracetylated glycopyranosyl thiosemicarbazones of acetophenones and benzaldehydes **3** were synthesized from corresponding tetra-*O*-acetyl-β-D-glycopyranosyl isothiocyanates **1** or **2** through tetra-*O*-acetyl-β-D-glycopyranosyl thiosemicarbazides **3** or **4** [7] (Schema 1, 2).

Condensation of tetra-*O*-acetyl-β-D-glycopyranosyl thiosemicarbazide **3** and **4** with a number of acetophenones and benzaldehydes afforded corresponding acetophenone and benzaldehyde (tetra-*O*-acetyl-β-D-glycopyranosyl)thiosemicarbazones **5** and **6**. This synthesis was carried out using minimum amount of solvent (ethanol) and deceased reaction

time comparing conventional heating methods (2-5 mL volume *versus* 15-20 mL, 2–5 min *versus* 60–90 min, respectively). Reaction time was from 2 min to 5 min depending substituent's nature: withdrawing substituents need shorter reaction time than donating ones. In the first period of reaction when reaction was starting to irradiate about 1-3 min, the pasty mixture of reagents in methanol was dissolved and the reaction became homogenous. In the final period of reaction, the solid product appeared and precipitated out. The products yields of microwave-asissted method were fairly high from 75% to 98%, while ones of conventional heating methods were 32%–81%. In some cases with acetophenones having *p*-Cl, *p*-NO_2 and *p*-Br groups, the yields attained 98%. The solid thiosemicarbazones **5** and **6** were filtered by suction and recrystallized from ethanol or ethanol/toluene (1:1 in volume). These compounds can dissolved in ethanol, toluene, chloroform, DMF,…and had high melting points. All the products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectra.

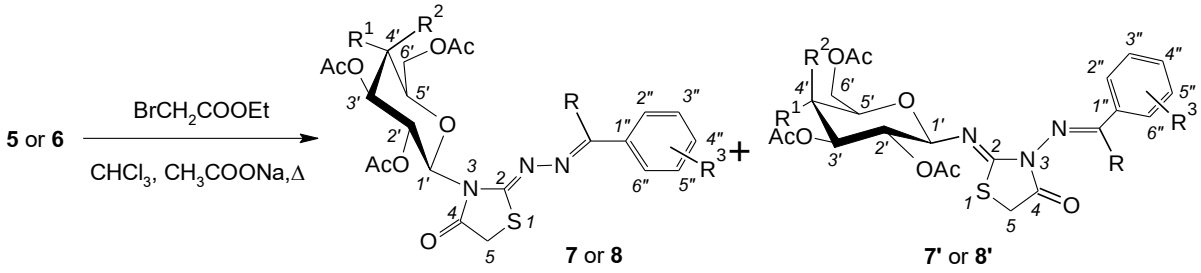


Scheme 1. Synthesis of tetra-*O*-acetyl-β-D-glycopyranosyl thiosemicarbazide **2**, where R^1=OAc, R^2=H: tetra-*O*-acetylglucopyranosyl (**1, 3**); R^1=H, R^2=OAc: tetra-*O*-acetylgalactopyranosyl (**2, 4**).



Scheme 2. Synthesis of peracetylated glycopyranosyl thiosemicarbazones **5** and **6**, R^3: see Tables 1, 2.

Per-*O*-acetyl-β-D-glycopyranosyl thiosemicarbazones **5** and **6** reacted with ethyl bromoacetate in the presence of anhydrous sodium acetate as catalyst in chloroform as solvent (Scheme 3). Because the initial thiosemicarbazones were asymmetrical, then two different 2-iminothiazolidin-4-one products **7** and **7'** or **8** and **8'** were formed in this reaction with various ratios. We realized that this reaction depended on the nature of solvent and on catalyst (Table 1). Optimal conditions for this reaction that were investigated in case of compound **7a** were as follows, solvent: chloroform, catalyst: anhydrous sodium acetate, reaction time: 8 h; then, reaction yield was 81% of 2-iminothiazolidin-4-ones **7a** and **7'a**. The ratios of these products **7** and **7'** or **8** and **8'** were estimated by ^{1}H NMR spectra.



Scheme 3. Conversion of 2,3,4,6-tetra-*O*-acetyl-β-D-glycopyranosyl thiosemicarbazones **5** and **6** into corresponding 2-iminothiazolidin-4-one compounds **7/7'** and **8/8'**.

Table 1. Influences of solvent and catalyst in reaction of 4'-nitroacetophenon (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazone **7a** with ethyl bromoacetate

Catalyst	Solvent, yield			
	Chloroform	**Ethanol**	**Dichloromethane**	**Toluene**
CH_3COONa	8 hrs, 81%	10 hrs, 70%	8 hrs, 73%	9 hrs, 75%
Et_3N	10 hrs, not formed	10 hrs, not formed	10 hrs, not formed	10 hrs, not formed
DABCO	10 hrs, not formed	10 hrs, not formed	10 hrs, not formed	10 hrs, not formed

The IR spectra of compounds **7** and **7'** or **8** and **8'** showed the characteristic bands in regions at 1732–1753 cm^{-1} ($\nu_{C=O}$ ester and $\nu_{C=O}$ lactam), 1223–1247 cm^{-1} and 1034–1044 cm^{-1} (ν_{C-O-C} ester), 1511–1602 cm^{-1} ($\nu_{C=C}$ in benzene ring), 1600–1618 cm^{-1} ($\nu_{C=N}$ imine). The appearance of absorption imine band at 1600–1618 cm^{-1} accompanied the absence of characteristic absorption stretching band of NH groups in thiosemicarbazone molecules in regions at 3323–3390 cm^{-1} and 3298–3332 cm^{-1} (Tables 2 and 3).

Table 2. Result in synthesis of 2-iminothiazolidin-4-one compounds (the pairs of **7** and **7'**)

Compound	R	Yield,%	m.p. ,°C	$\nu_{C=O}$	$\nu_{C=N}$	ν_{C-S}	ν_{C-O-C}
7a & **7a'**	4-NO_2	81	137–138	1751	1610	1366	1226, 1037
7b & **7b'**	3-NO_2	75	143–143	1747	1618	1370	1229, 1034
7d & **7d'**	3-NO_2-4-OMe	75	153–155	1753	1613	1368	1224, 1039
7f & **7f'**	3-NO_2-4-Cl	79	154–155	1753, 1732	1614	1368	1226, 1044
7h & **7h'**	4-Cl	72	154–158	1752	1613	1367	1234, 1040
7i & **7i'**	4-Br	77	152–164	1744	1611	1367	1227, 1040
7j & **7j'**	H	70	157–159	1743	1613	1368	1247, 1036
7k & **7k'**	4-Me	74	159–161	1745	1613	1365	1232, 1039
7l & **7l'**	4-OMe	72	138–140	1743	1612	1368	1252, 1035
7p & **7p'**	4-OH	73	184–187	1741	1600	1368	1223, 1034

Table 3. Result in synthesis of 2-iminothiazolidin-4-one compounds (the pairs of **8** and **8'**)

Compound	R	Yield,%	m.p. ,°C	$\nu_{C=O(lactam)}$	$\nu_{C=O(este)}$	$\nu_{C-O-C(este)}$	$\nu_{C=C\ (thơm)}$
8a & **8a'**	4-NO_2	85	223–224	1627	1746	1228;1039	1597;1554
8b & **8b'**	3-NO_2	79	214–215	1624	1745	1233; 1039	1560;1530
8d & **8d'**	4-Cl	86	216–217	1619	1743	1243;1089	1575;1554
8f & **8f'**	4-F	77	184–185	1619	1749	1231;1039	1595
8h & **8h'**	H	80	201–202	1622	1746	1237;1043	1582;1563
8i & **8i'**	4-iPr	82	150–151	1618	1744	1229;1035	1579
8j & **8j'**	4-Me	76	205–206	1616	1743	1228; 1033	1578;1551
8k & **8k'**	4-OMe	75	166–167	1622	1746	1249; 1083	1588
8l & **8l'**	4-OH	84	172–173	1613	1748	1230;1036	1588;1564
8p & **8p'**	4-NMe_2	78	172–173	1606	1744	1229;1040	1529

From Tables 4 and 5, the ^{1}H NMR showed resonance signals of protons in monosaccharide moiety of the pairs 7/**7'** or **8**/**8'** at δ 4.0–6.5 ppm, and protons in benzene ring at 7.0–8.5 ppm, simultaneously, resonance signal in doublet of proton NH-4 at 9.00–8.43 ppm and resonance signal in singlet of proton NH-2 at 12.17–11.84 ppm in thiosemicarbazone molecules disappeared in their ^{1}H NMR spectra. Other evidence that confirmed the formation of 2-iminothiazolidin-4-one ring was the appearance of resonance at 4.15–4.04 ppm (multiple) and 3.90–3.85 ppm (doublet, ^3J = 18.75–17.0 Hz). The value of coupling constants ^3J = 18.75–17.0 Hz accorded with the one of normal H–H-*geminal* coupling. Especially, resonance signals of proton H-1' and H-5' in pyranose ring were clearly separated into two group. For 2-iminothiazolidin-4-one isomer **7** or **8**, chemical shift of proton H-1' showed at δ = 6.07–6.05 ppm, and proton H-2' was at δ = 5.89–5.87 ppm; whereas, for 2-iminothiazolidin-4-one isomer **7'** or **8'**, resonance signals of these protons showed at δ = 5.91–5.89 ppm (H-1') and δ = 6.21–6.18 ppm (H-2'), respectively. Isomeric ratios of **7** /**7'** or **8**/**8'** were ~3:1. ^{13}C NMR in the pairs of isomers **5/5'** represented in Table 6**.**

Table 4. ^{1}H NMR spectral data [δ, (ppm), multiplicity and *J* (Hz)] of 2-iminothiazolidin-4-one compounds (for isomer **7** only)

R	4-NO_2	3-NO_2	4-OMe-3-NO_2	4-Cl-3-NO_2	4-Cl
	7a	**7b**	**7d**	**7f**	**7h**
H-1'	5.92, d, 9.0	5.93, d, 9.0	5.91, d, 9.0	5.95, d, 9.0	5.91, d, 9.0
H-2'	6.18, t, 9.5	6.18, t, 9.5	6.18, t, 9.5	6.16, t, 9.25	6.19, t, 9.25
H-3'	5.52, t, 9.5	5.54, t, 9.5	5.52, t, 9.5	5.52, t, 9.5	5.52, t, 9.75
H-4'	5.04, t, 9.25	5.04, t, 10	5.03, t, 10	5.03, t, 10.0	5.02, t, 10.0
H-5'	4.33-4.31, m	4,33, ddd, 10.0, 4.5, 2.0	4.32, ddd, 9.75, 4.5, 2.0	4.32, ddd, 10.0, 4.5, 2.0	4.32, ddd, 2.0, 4.5, 2.0
H-5a	4.10-4.04, m	4.15-4.04, m	4.08-4.03, m	4.15-4.03, m	4.08-4.03, m
H-5b	3.92, d, 18.75	3.92, d, 17.5	3.90, d, 18.75	3.91, g, 17.0	3.91, d, 18.75
H-6'a	4.12-4.17, m	4.19, dd, 12.5,4.5	4.17, dd, 12.5,4.0	4.18, dd, 11.75,4.25	4.17, dd, 12.5,4.0
H-6'b	4.1-4.04, m	4.15-4, 04, m	4.08-4.03, m	4.15-4.03, m	4.08-4.03, m
H-2"	8.12, d, 8.5	8.67, s	8.33, d, 2.0	8.47, d, 2.0	7.90, d, 8.5
H-3"	8.3, d, 8.5	-	-	-	7.53, d, 8.5
H-5"	8.3, d, 8.5	7.77, t, 8.0	7.46, d, 9.0	7.88, d, 8.5	7.53, d, 8.5
H-6"	8.12, d, 8.5	8.32-8.29, m	8.16, dd, 9.0	8.16, dd, 8.5	7.90, d, 8.5
H-4"	-	8.32-8.29, m	-	-	-
CO*CH_3*	2.16-1.93, s	2.02, 1.91, s	2.02-1.91, s	2.01-1.90, s	2.01-1.90, s
N=C–*CH_3*	2.55, s	2.53, s	2.52, s	2.53, s	2.49, s
R	**4-Br**	**H**	**4-Me**	**4-OMe**	**4-OH**
	7i	**7j**	**7k**	**7l**	**7p**
H-1'	5.90, d, 9.0	5.90, d, 9.0	5.91, d, 9.0	5.9, d, 9.0	5.89, d, 9.5
H-2'	6.19, t, 9.25	6.21, t, 9.25	6.21, t, 9.25	6.20, t, 9.25	6.2, t, 9.25
H-3'	5.52, t, 9.5	5.52, t, 9.75	5.52, t, 9.5	5.51, t, 9.5	5.50, t, 9.75
H-4'	5.03, t, 10.0	5.03, t, 10.0	5.03, t, 10.0	5.03, t, 10.0	5.02, t, 10.0
H-5'	4.32, ddd, 10.0, 4.5, 2.0	4.31, ddd, 10.0, 4.5, 2.0	4.30, ddd, 9.5, 4.5, 2.0	4.30, ddd, 10.0, 4.5, 2.0	4.30, ddd, 10.0, 4.5, 2.0
H-5a	4.07-4.04, m	4.09-4.01, m	4.1-4.01, m	4.09-4.03, m	4.09-4.01, m
H-5b	3.91, d, 17.5	3.89, d, 17.0	3.89, d, 18.75	3.88, d, 18.75	3.85, d, 17.5
H-6'a	4.17, dd, 12.5,4.0	4.17, dd, 12.5,4.0	4.17, dd, 12.5,4.0	4.16, dd, 12.5,4.0	4.16, dd, 12.5,4.0
H-6'b	4.07-4.04, m	4.09-4.01, m	4.10-4.01, m	4.09-4.03, m	4.09-4.01, m
H-2"	7.82, d, 8.5	7.47-7.46, m	7.79, d, 9.0	7.85, d, 9.25	7.75, d, 9.25
H-3"	7.66, d, 8.5	-	7.27, d, 9.0	6.82, d, 9.25	6.82, d, 9.25

H-5”	7.66, d, 8.5	-	7.27, d, 9.0	6.82, d, 9.25	6.82, d, 9.25
H-6”	7.82, d, 8.5	7.47-7.46, m	7.79, d, 9.0	7.85, d, 9.25	7.75, d, 9.25
H-4”	-	7.47-7.46, m	-	-	-
CO*CH*$_3$	2.02-1.92, s	2.01-1.93, s	2.02-1.93, s	2.01-1.90, s	2.01-1.88, s
N=C–*CH*$_3$	2.48, s	2.50, s	2.56, s	2.46, s	2.43, s

Table 5. ^{1}H NMR spectral data [δ, (ppm), multiplicity and *J* (Hz)] of 2-iminothiazolidin-4-one compounds (for **6/6’**)

Proton	4-NO_2		4-Cl		4-CH_3		4-OMe	
	8a	**8’a**	**8c**	**8’c**	**8e**	**8’e**	**8h**	**8’h**
-CH=N	8.71,s	8.70, s	8.56,s	8.54,s	8.49,s	8.49,s	8.46,s	8.46,s
H-2’’, H-6’’	8.10,d,8.5	8.06,d,8.5	7.87,d,8.25	7.82,d,8.25	7.73, d, 8.25	7.49–7.48,m	7.79,d,8.25	7.75,d,8.25
H-3’’,H-5’’	8.33,d,8.5	8.33,d,8.5	7.56,d,8.25	7.56,d,8.25	7.29,d, 8.25	7.85–7.80,m	7.04,d,8.25	7.04,d,8.25
H-1’	5.92,d,9.5	6.03,d,9.5	5.90,d,9.5	6.01,d,9.5	5.89,d,9.0	6.01,d,9.0	5.88,d,9.5	5.99,d,9.0
H-2’	6.20,t,9.5	5.92,t,9.5	6.20,t,9.5	5.89,t,7.5	6.21,t,9.5	5.87,t,9.25	6.21,t,9.25	5.86,d,9.5
H-3’	5.52,t,9.5	5.51,t,9.5	5.51,t,9.75	5.49.t,9.75	5.51,t,9.75	5.51,t,9.75	5.50,t,9.75	5.50,t,9.75
H-4’	5.01,t,9.25	4.98,t,8.5	5.00,t,10.0	4.98,t,9.75,	5.01,t,9.75	4.97,t,9.75	5.00,t,10.0	4.96,t,7.0
H-5’	4.31,m	4.31,m	4.29,m	4.29,m	4.29,m	4.29,m	4.28,m	4.28,m
H-6’a	4.11,dd	4.11,dd	4.14,dd	4.14,dd	4.15,dd	4.14,dd	4.14,dd	4.14,dd
H-6’b	4.09,dd	4.09,dd	4.08,dd	4.08,dd	4.11,dd	4.08,dd	4.10,dd	4.08,dd
H-5	4.14,s	4.07 & 3.95,d	4.10,s	4.07 & 3.93,d	4.09,s	4.05 & 3.89,d	4.08,s	4.053& 3.88,d
$COCH_3$	2.03– 1.92,m,3H	2.03– 1.92,m,3H	2.03– 1.91,m,3H	2.03– 1.91,m,3H	2.03– 1.90,m,3H	2.03– 1.90,m,3H	2.03– 1.91,m,3H	2.03– 1.91,m,3H
Other Proton							3.82,s (OC*H*$_3$)	3.82,s (OC*H*$_3$)

Table 6. ^{13}C NMR spectral data (δ, ppm) of 2-iminothiazolidin-4-one compounds (for isomer **7** only)

R	4-NO_2	3-NO_2	4-Cl-3-NO_2	4-OMe-3-NO_2	4-Cl	4-Br	H	4-Me	4-OMe	4-OH
	7a	**7b**	**7d**	**7f**	**7h**	**7i**	**7j**	**7k**	**7l**	**7p**
C-1'	79.6	79.6	79.5	79.5	79.5	79.5	79.6	79.5	79.5	79.5
C-2'	67.3	67.2	67.8	67.2	67.2	67.2	67.3	67.2	67.2	67.3
C-3'	72.7	72.6	72.6	72.6	67.6	72.7	72.7	72.7	72.7	72.8
C-4'	67.2	67.2	67.8	67.1	67.1	67.1	67.2	67.1	67.1	67.2
C-5'	72.8	72.8	72.7	72.7	72.7	72.7	72.8	72.7	72.7	72.8
C-6'	61.4	61.4	61.4	61.4	61.4	61.4	61.4	61.4	61.4	61.5
C-1'''	148.2	148.0	137.7	129.7	136.2	136.5	152.4	139.9	129.8	157.5
C-2'''	127.8	130.1	123.3	122.9	128.3	128.5	137.9	126.5	128.2	128.3
C-3'''	123.6	130.1	147.7	139.5	128.5	131.4	128.9	129.0	113.8	115.3
C-4'''	148.2	124.5	131.3	153.2	136.2	123.7	130.6	139.9	160.9	160.3
C-5'''	123.6	120.8	131.8	115.3	128.5	131.4	128.9	129.0	113.8	115.3
C-6'''	127.8	139.0	137.7	132.3	128.3	128.5	137.9	126.5	128.2	128.3
C=O	171.6	171.6	171.6	171.6	171.6	171.6	171.6	171.6	171.6	171.6
$COCH_3$	20.4-20.2	20.4-20.2	20.4-20.2	20.4-20.2	20.4-20.2	20.4-20.2	20.4-20.2	20.4-20.2	20.4-20.2	20.4-20.2
N=C-CH_3	15.0	14.9	14.7	14.7	14.8	14.8	15.0	14.9	14.8	14.8

3. Experimental

Melting points were determined by open capillary method on STUART SMP3 instrument (BIBBY STERILIN-UK) and are uncorrected. IR spectra (KBr disc) were recorded on a Impact 410 FT-IR Spectrometer (Nicolet, USA). ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance Spectrometer AV500 (Bruker, Germany) at 500.13 MHz and 125.77 MHz, respectively, using DMSO-d_6 as solvent and TMS as an internal standard. All the starting materials and reagents were purchased from commercial suppliers and used no further purification. 2,3,4,6-Tetra-*O*-acetyl-β-D-glycopyranosyl isothiocyanates **1** and **2** were prepared by the reaction of per-*O*-acetyl-β-D-glucopyranosyl bromide (prepared from D-glucose) with lead thiocyanate in dried toluene and 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl thiosemicarbazide **3** and **4** were synthesized by known method [5].

General procedure for synthesis of substituted acetophenone and benzaldehyde tetra-O-acetyl-β-D-glycopyranosyl thiosemicarbazones (**5** and **6**). A suspension mixture of (tetra-*O*-acetyl-β-D-glycopyranosyl)thiosemicarbazide **3** or **4** (1 mmol) and corresponding substituted acetophenone (1 mmol) and glacial acetic acid (0.05 mL) in absolute ethanol (2–5 mL) was irradiated with reflux for 2-5 minutes in microwave oven. After reaction the mixture was cooled to room temperature, the colorless crystals were filtered with suction. The crude product was recrystallized from ethanol or ethanol/toluene to yield corresponding acetophenone (2,3,4,6-tetra-*O*-acetyl-β-D-glycopyranosyl)thiosemicarbazones **5** and **6**.

General procedure for conversion of substituted acetophenone tetra-O-acetyl-β-D-glucopyranosyl thiosemicarbazones (**5** and **6**) *into 2-iminothiazolidin-4-one compounds* (**7**/**7'**

and **8**/**8'**). To a suspension mixture of per-*O*-acetyl-β-D-glucopyranosyl thiosemicarbazone **5** or **6** (2.5 mmol) and anhydrous sodium acetate (0.5 g) in dried chloroform (35 mL) was added a solution of ethyl bromoacetate (0.42 mL) in chloroform (15 mL) with stirring. After stirring for 30 min at room temperature, reaction mixture was heated with reflux for 8-10 hrs. Removed the solvent at reduced pressure, then washed with water (2-3 times) and recrystallized from 95% ethanol to afford the title compounds **7/7'** or **8/8'.**

4. Conclusion

We have developed a highly efficient method for the synthesis and conversion of (2,3,4,6-tetra-O-acetyl-β-D-glycopyranosyl)thiosemicarbazones of benzaldehydes and acetophenones.

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