SYNTHESIS OF AROMATIC (PER-*O*-ACETYL-β-LACTOSYL)-THIOSEMICARBAZONES

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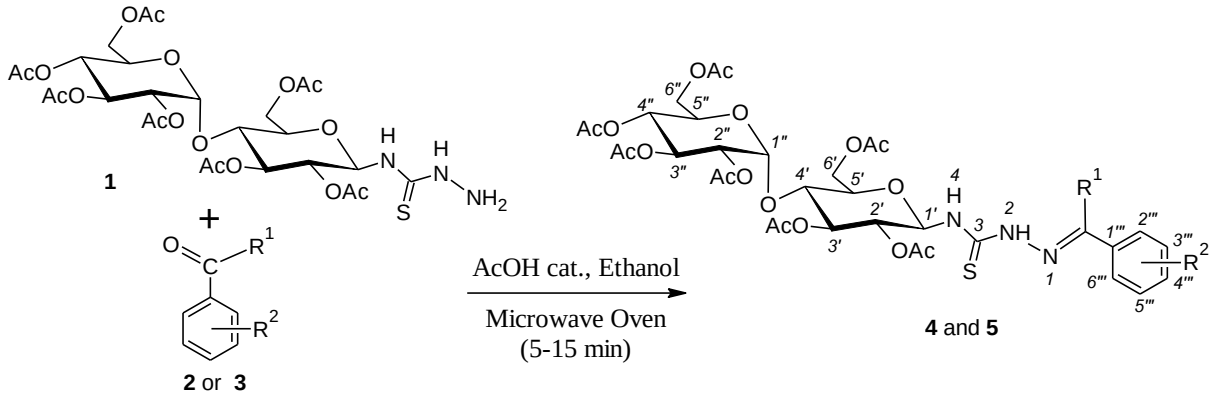
Abstract. A series of per-*O*-acetyl-β-D-glycosyl thiosemicarbazones **4** and **5** of benzaldehydes and acetophenones were obtained from reaction of per-*O*-acetyl-β-maltosyl thiosemicarbazide **1** with corresponding carbonyl compounds (**2** and **3**) in ethanol or acetic acid as solvent using microwave-assisted method. The positions of the magnetic resonance signals in their NMR spectra and the substituent's nature have been indicated by Hammett's regression. The β anomeric configuration of these thiosemicarbazones was confirmed on the basis of the coupling constant J = 9.0–9.5 Hz between proton NH-4 of thiosemicarbazone bond and proton H-1' in maltose component. Structures of thiosemicarbazones were confirmed by spectroscopic methods.

1. INTRODUCTION

The chemistry of isothiocyanate derivatives of saccharides is extensively elaborated and well documented [1, 2]. These compounds arouse interest as versatile intermediates for preparing various (e.g., heterocyclic) derivatives. Several isothiocyanates of monosaccharides (e.g., of D-glucose and D-galactose) have been synthesized [1, 2] and transformed into thiosemicarbazide compounds [3]. Sugar isothiocyanates[1] have proven to be useful synthons in the preparation of a variety of *N*- and *neo*-*N*-glycoconugates [4], such as nucleosides [5], *N*-glycosyl compounds [6], or *N*-glycopeptides [7–9]. In addition, the high reactivity of the isothiocyanate functionality towards nucleophiles and its ability to undergo reductive or oxidative transformations allow easy access to other functional groups including amide, thiourea, thiocarbamate, dithiocarbamate, thioformamide [10], isonitrile [11], dichloroisonitrile [12], and isocyanate derivatives [13], which may be used for further transformations.

2. RESULTS AND DISCUSSION

We have previously reported the synthesis of several peracetylated glycopyranosyl isothiocyanates and their reactivity with N-nucleophiles to yield a novel series of peracetylated glucopyranosyl thioureas and substituted benzaldehyde and acetophenone peracetylated-*O*-glycopyranosyl thiosemicarbazones [14–17]. We now report here for the first time the synthesis and characterization of hepta-*O*-acetyl-β-maltosyl thiosemicarbazide from peracetylated maltosyl isothiocyanate and its reaction with a series of aromatic aldehydes as shown in Scheme 1.



Scheme 1. Synthetic pathway for per-*O*-acetyl-β-maltosyl thiosemicarbazones of benzaldehydes (**2:** R=H) and acetophenones (**3**: R=CH_3); R^1 and R^2 in **4** and **5:** see Table 1.

Table 1. Substituted benzaldehyde and acetophenone (hepta-*O*-acetyl-β-maltosyl)-thiosemicarbazones **4** & **5**

Entry	R^2	mp (ºC)	Yield %	Solvent	IR Spectra (cm^{-1})				
					ν_{NH}	$\nu_{C=N}$	$\nu_{C=O}$	ν_{COC}	$\nu_{C=S}$
(**4**), *R^1=H*									
4a	4-NO_2	150-151	53	Ethanol	3324,3137	1595	1747	1228,1044	1369
4b	3-NO_2	210-211	81	Ethanol	3324,3147	1605	1747	1228,1044	1368
4c	4-Cl	197-198	59	Ethanol	3326,3145	1605	1747	1228,1054	1369
4d	2,4-diCl	118-119	86	Acetic acid	3324,3146	1589	1747	1228,1044	1369
4e	4-Br	204-205	85	Acetic acid	3324,3145	1595	1746	1226,1054	1368
4f	H			Ethanol	3291,3171	1605	1746	1235,1048	1374
4g	4-iPr	127-128	53	Acetic acid	3329,3139	1611	1747	1238,1054	1369
4h	3-OMe	184-185	54	Ethanol	3298,3130	1590	1746	1240,1044	1369
4i	3-OEt-4-OH	191-192	69	Ethanol	3334,3147	1599	1747	1244,1044	1368
4j	4-OH	117-118	55	Ethanol	3334,3147	1612	1747	1244,1044	1368
4k	3-OH	178-179	70	Ethanol	3324,3147	1600	1746	1228,1044	1369
4l	2-OH	128-129	86	Ethanol	3349	1610	1746	1230,1038	1375
(**5**), *R^1=CH_3*									
5a	4-NO_2	199-200	85	Ethanol	3494,3338	1602	1747	1232,1041	1374
5b	3-NO_2	164-165	58	Acetic acid	3477,3307	1605	1749	1233,1041	1373
5c	3-NO_2-4-Br	178-179	71	Acetic acid	3477,3307	1611	1749	1234,1041	1373
5d	3-NO_2-4-OMe	198-199	65	Ethanol	3551,3317	1620	1748	1239,1042	1370
5e	3-NO_2-4-OEt	210-211	75	Ethanol	3386,3315	1622	1754	1223,1036	1377
5f	4-Cl	188-189	45	Acetic acid	3483,3304	1602	1746	1231,1044	1376
5g	4-Br	192-193	70	Ethanol	3379,3308	1619	1758	1225,1041	1372
5h	H	165-166	51	Ethanol	3469,3311	1622	1745	1233,1045	1369
5i	4-Me	192-193	51	Ethanol	3476,3304	1621	1744	1231,1043	1370
5j	4-OH	160-161	49	Ethanol	3456,3334	1611	1749	1240,1040	1372
5k	4-OMe	190-191	67	Ethanol	3378,3328	1602	1744	1263,1023	1377

Table 2. Summary of ^{1}H NMR spectral data of compounds **4** and **5**

Proton	δ (ppm)	Multiplicity	*J* (Hz)	Proton	δ (ppm)	Multiplicity	*J* (Hz)
H-4	8.92–8.64	d	9.5–9.0	**H-3"**	5.28–5.14	t	10.0–9.25
H-2	12.18–10.97	s	-	**H-4"**	5.02–4.99	t	10.0–9.75
H_{imine}	8.18-8.01	s	-	**H-5"**	4.90–4.87	dd	4.0–3.5, ~10.5
H-1'	5.94–5.81	t	9.25–9.0	**H-6"a**	4.39–4.34	dd or d	12.25–10.0, 2.25–2.0

Proton	δ (ppm)	Multiplicity	*J* (Hz)	Proton	δ (ppm)	Multiplicity	*J* (Hz)
H-2'	5.25–5.15	m or t	10.0–9.25	**H-6"b**	4.21–4.19	dd or m	13.0–12.0, 5.0–4.25
H-3'	5.45–5.41	d or t	9.25–9.0	**H-2"'**	8.25–7.14	d	9.0–8.5
H-4'	3.96–3.92	d or m	9.75–9.0	**H-3"'**	8.11–6.81	d	9.0–8.5
H-5'	4.02–3.92	m	-	**H-4"'**	8.25–6.83	dt or dd	4.0–1.5, 8.25–8.0
H-6'a	4.22–4.16	d	5.0–4.75, 13.0–10.0	**H-5"'**	8.11–6.81	d or t	9.0–7.21
H-6'b	4.06–3.97	m	-	**H-6"'**	8.39–7.12	d, dd, or t	2.0–1.75, 9.0–7.25
H-1"	5.34–5.32	d	4.0–3.5	**MeCO**	2.06–1.91	s	
H-2"	4.06–3.97	m	-	***CH*$_3$C=N**	2.40–2.36	s	-

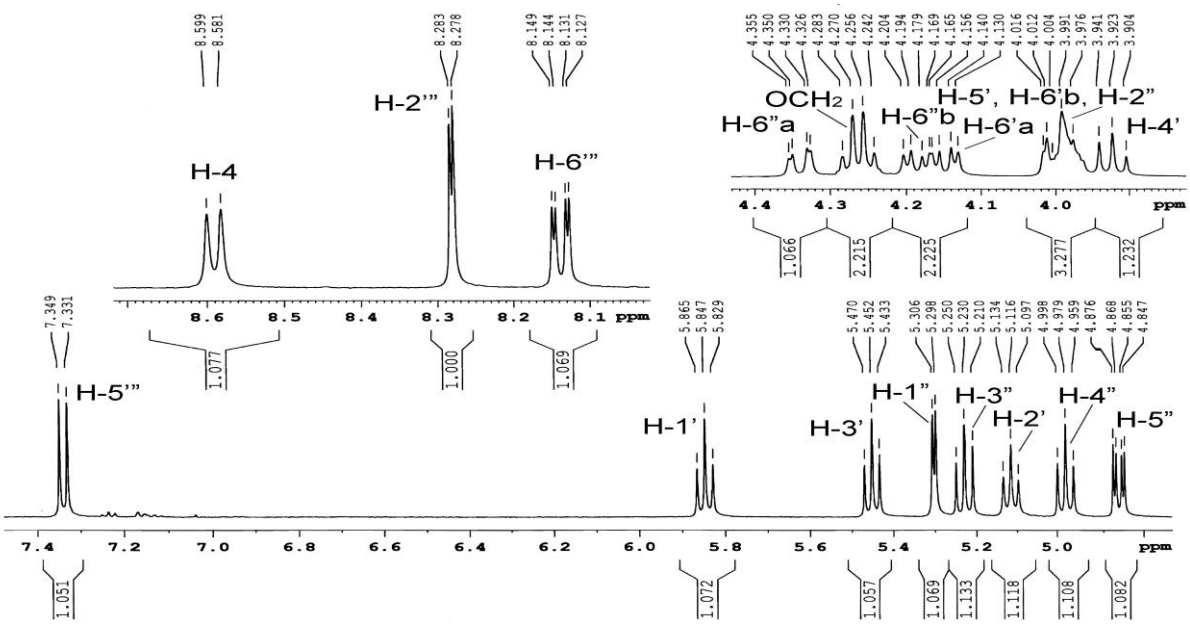


Figure 1. ^{1}H NMR spectrum of benzene ring and sugar moiety of compound **5** (R=4-OEt-3-NO_2).

The ^{13}C-NMR spectrum of compound **4** and **5** showed resonance signals at δ 179.7–177.8 ppm (carbon atom in C=S group), δ 171.0–169.1 ppm (carbon atoms in C=O bond of acetyl groups), δ 159.7–115.5 ppm (benzene ring), δ 96.3–62.8 ppm pyranose rings) and δ 21.7–20.2 ppm (methyl-carbons in acetyl groups).

Proton of azomethine bond in benzaldehyde series **4** shows a sharp peak at δ 8.18–8.01 ppm (CH=N) in singlet. It's indicated that the nature of the substituents on benzene ring affected evidently to the position of this signal. This effect could be represented by Hammett's regression as follows: $\delta_{C\boldsymbol{H}=N} = 0.15\sigma + 8.06$ (with regression coeffient R^2=0.78). The parameter was small, $\rho = 0.15$, it means that the donating or withdrawing capacity of the substituents had unremarkable effects to this resonance position (Fig. 2, upper right). Similarly, the positions of resonance signals of protons NH-2 and NH-4 (in benzaldehyde and acetophenone series) had linear regression expressions as follows, respectively: $\delta_{NH-2} = 0.31\sigma + 11.90$ ($R^2 = 0.93$), $\delta_{NH-4} = 0.34\sigma + 8.64$ ($R^2 = 0.92$) (for benzaldehyde series) and $\delta_{NH-2} = 0.25\sigma + 10.77$ ($R^2 = 0.92$), $\delta_{NH-4} = 0.22\sigma + 8.52$ ($R^2 = 0.98$) (for acetophenone series). The parameters were relative large, $\rho = 0.31$ and 0.34 (for NH-1 and NH-4, respectively, in benzaldehyde series) and $\rho = 0.25$ and 0.22 (for NH-2 and NH-4, respectively, in

acetophenone series) which indicated that the donating or withdrawing capacity of the substituents had noticeable effects to these resonance positions (Fig. 2, Table 5).

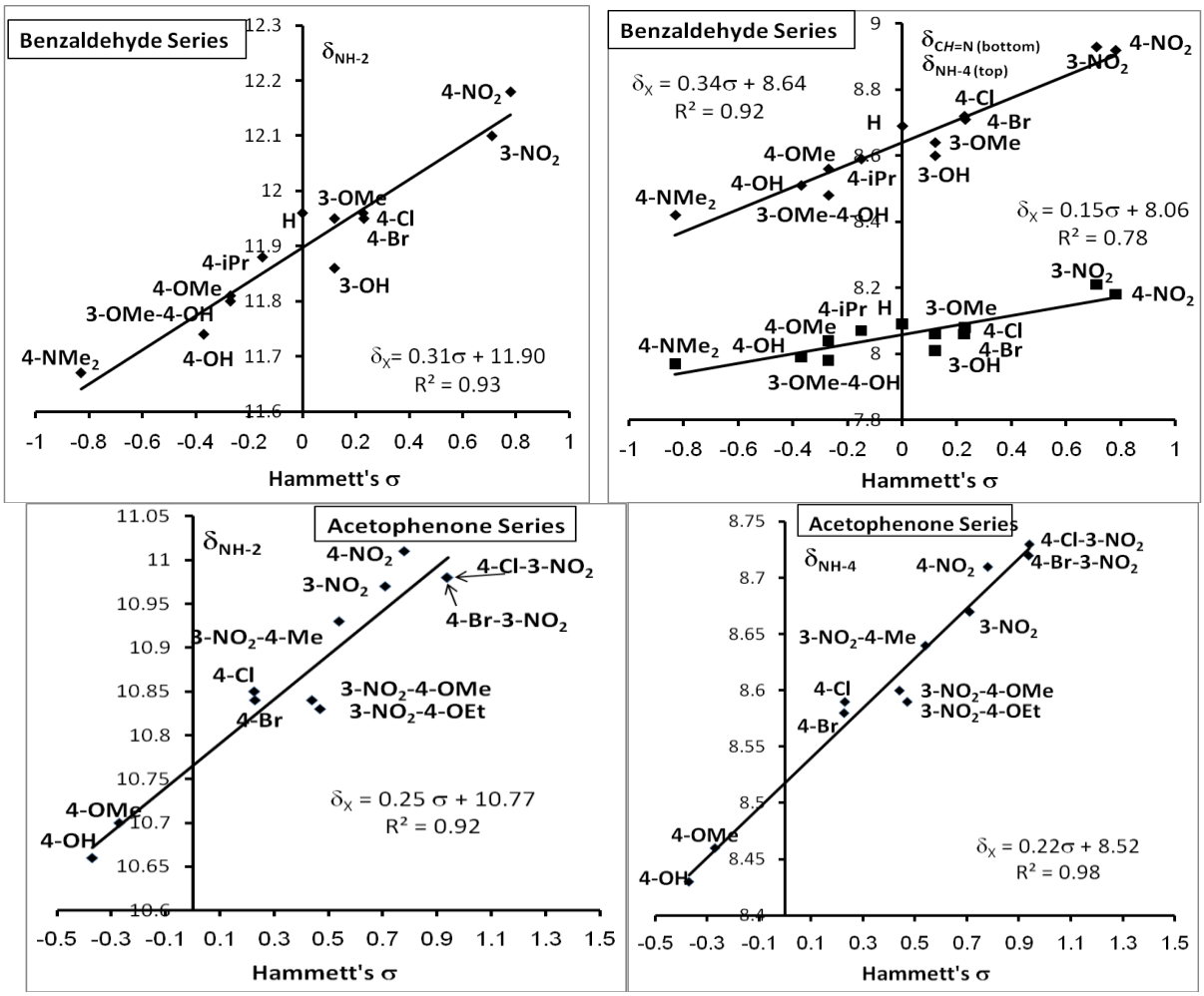


Figure 2. Linear relationships of δ_{NH-2}, δ_{NH-4} and $\delta_{CH=N}$ and Hammett's σ in compouds **4** and **5.**

Table 3. Summary of ^{13}C NMR spectral data of compounds **4** and **5**

Carbon	δ (ppm)	Carbon	δ (ppm)
C=S	179.7–177.8	**C-1'**	82.1–81.1
$COCH_3$	171.0–169.1	**C-2'**	69.8–68.9
CH=N	147.6–141.1	**C-3'**	75.6–74.3
C-1'''	142.1–124.7	**C-4'**	74.7–73.7
C-2'''	129.3–111.3	**C-5'**	73.8–72.9
C-3'''	147.1–124.7	**C-6'**	62.3–61.5
C-4'''	159.7–148.8	**C-1"**	96.3–95.3
C-5'''	130.7 –115.5	**C-2"**	69.0–67.9
C-6'''	139.4–118.7	**C-3"**	72.3–71.1
$COCH_3$	21.7–20.2	**C-4"**	68.7–67.8
		C-5"	70.4–69.5
		C-6"	63.8–62.8

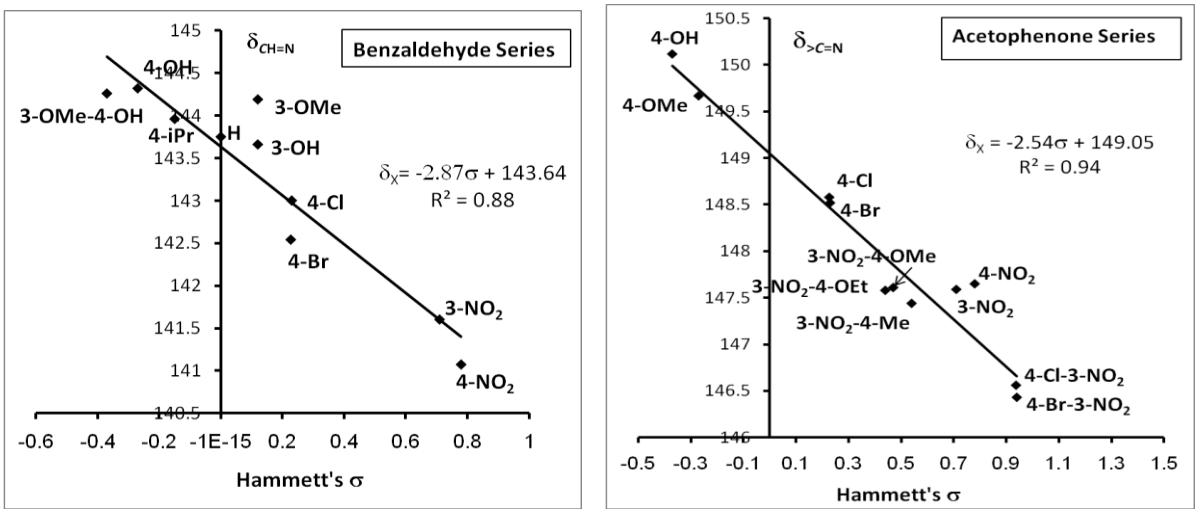


Figure 3. Relationships between $\delta_{CH=N}$ and $\delta_{>C=N}$ and Hammett's σ in compouds **4** and **5.**

Conversely, carbon atom in imine group were affected clearly by these substituents with opposite trend: the donating ones (with $\sigma < 0$, such as 4-NMe_2, 4-OH, 4-OMe, 4-Me in benzaldehyde series, or 4-OMe, 4-OH in acetophenone series) caused signal to be shifted upfield, and the withdrawing ones (with $\sigma < 0$, such as 4-F, 4-Br, 4-Cl and 3-OMe, 3-OMe-4-OH in benzaldehyde series, or or 4-Me-3-NO_2, 4-OEt-3-NO_2, 4-OMe-3-NO_2, 4-Cl-3-NO_2, 4-Br-3-NO_2, 4-NO_2, 3-NO_2, 4-Cl, 4-Br in acetophenone series) caused the resonance of this carbon atom to shift downfield. These tendencies could be shown in equations as follows: $\delta_{CH=N} = -2.87\sigma + 143.64$ ($R^2 = 0.88$) (for benzaldehyde series) and $\delta_{>C=N} = -2.54\sigma + 149.05$ ($R^2 = 0.94$) (for acetophenone series), the parameter was $\rho < 0$, it mean that the opposite influence of the substituents to resonance position in this case. The large values of parameters ρ indicated that the electron nature of the substituents in benzene ring governed remarkably the resonance positions of carbon atoms in C=N bond of these thiosemicarbazones (Fig. 3).

Table 4. Summary of ^{13}C NMR spectral data of compounds 4 and **5**

Carbon	δ (ppm)	Carbon	δ (ppm)
C=S	179.7–177.8	**C-1'**	82.1–81.1
***C*OCH$_3$**	171.0–169.1	**C-2'**	69.8–68.9
CH=N	147.6–141.1	**C-3'**	75.6–74.3
C-1'''	142.1–124.7	**C-4'**	74.7–73.7
C-2'''	129.3–111.3	**C-5'**	73.8–72.9
C-3'''	147.1–124.7	**C-6'**	62.3–61.5
C-4'''	159.7–148.8	**C-1"**	96.3–95.3
C-5'''	130.7 –115.5	**C-2"**	69.0–67.9
C-6'''	139.4–118.7	**C-3"**	72.3–71.1
		C-4"	68.7–67.8
		C-5"	70.4–69.5
		C-6"	63.8–62.8
		COC*H*$_3$	21.7–20.2

Table 5. Hammett's relationships between chemical shifts and substituent's constans σ of compounds **4** and **5**

R	σ	δ_{NH-1}	δ_{NH-3}	$\delta_{>C=N}$	δ_{NH-1}	δ_{NH-3}	$\delta_{CH=N}$	$\delta_{CH=N}$
		Acetophenone series 4			**Benzaldehyde series 5**			
4-Me-3-NO_2	0.54	10.93	8.64	147.44				
4-OEt-3-NO_2	0.47	10.83	8.59	147.61				
4-OMe-3-NO_2	0.44	10.84	8.60	147.58				
4-Cl-3-NO_2	0.94	10.98	8.73	146.43				
4-Br-3-NO_2	0.937	10.98	8.72	146.56				
4-NO_2	0.78	11.01	8.71	147.65	12.18	8.92	8.18	141.07
3-NO_2	0.71	10.97	8.67	147.59	12.10	8.93	8.21	141.60
4-Cl	0.23	10.84	8.59	148.52	11.95	8.71	8.08	143.00
4-Br	0.227	10.85	8.58	148.58	11.96	8.72	8.06	142.54
4-OMe	-0.27	10.70	8.46	149.67	11.80	8.56	8.04	-
4-OH	-0.37	10.66	8.43	150.12	11.74	8.51	7.99	144.26
3-OH	0.12				11.86	8.60	8.01	144.19
3-OMe	0.12				11.95	8.64	8.06	143.66
H	0.00				11.96	8.69	8.09	143.75
4-iPr	-0.15				11.88	8.59	8.07	143.96
3-OEt-4-OH	-0.27				11.81	8.48	7.98	144.32
4-NMe_2	-0.83				11.67	8.42	7.97	-

3. EXPERIMENTAL

Melting points were determined on a STUART SMP3 apparatus (BIBBY STERILIN-UK). The IR spectra were recorded on a Magna 760 FT-IR Spectrometer (NICOLET, USA) in KBr disc. The ^{1}H NMR (at 500.13 MHz) and ^{13}C NMR (at 125.77 MHz) spectra were recorded on an AVANCE Spectrometer AV500 (BRUKER, Germany) in DMSO-d_6 solution in ppm compared to TMS as internal reference.

General synthetic procedure of substituted benzaldehyde and acetophenone (hepta-O-acetyl-β-maltosyl)-thiosemicarbazones (**4** and **5**). A mixture of hepta-*O*-acetyl-β-maltosyl thiosemicarbazide **1** (1 mmol), benzaldehyde **2** or acetophenones **3** (1 mmol) and glacial acetic acid (0.5 mL) in absolute ethanol or glacial acetic acid (5–10 mL) was heated at reflux using domestic microwave oven TIFANY 750W in 5-15 min. In case of ethanol as solvent, the solvent was evaporated to one half the original volumes. The resulting colorless crystals were filtered by suction. In case of acetic acid as solvent, the water was added, and then the precipitate was filtered by suction, washed until pH 7. The crude product was recrystallized from 95% ethanol to afford the title compounds **4** or **5**.

4. CONCLUSION

We have developed a highly efficient method for the synthesis of hepta-*O*-acetyl-β-maltosyl thiosemicarbazide and its conversion to corresponding thiosemicarbazones with substituted benzaldehydes and acetophenones under microwave-assisted heating conditions.

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REFERENCES

1. Witczak, Z., Monosaccharide isothiocyanates and thiocyanates: Synthesis, Chemistry, and Preparative Applications. In *Advances in Carbohydrate Chemistry and Biochemistry*, Tipson, R.S., Ed.; Academic Press: New York, 1986; Vol. 44, pp. 91-145.

2. (a) García-Fernández, J. M.; Ortiz-Mellet, C., *Sulfur Rep.* **1996**, *19*, 61-169. (b) García-Fernández, J. M.; Ortiz Mellet, C., Chemistry and developments of N-thiocarbonyl carbohydrate derivatives: sugar isothiocyanates, thioamides, thioureas, thiocarbamates, and their conugates. In *Advances in Carbohydrate Chemistry and Biochemistry*, Horton, D., Ed.; Academic Press: New York, 2000; Vol. 55, pp. 35-135.
3. Tashpularov, A. A.; Afanasev, V. A.; Lidaks, M.; Sukhova, N. M.; Popelis, J. and Rakhmatullaev, *J. Khim. Geterontkl. Soedin.* **1983**, 170-174; *Chem. Abstr.* **1983**, *99*, 22818u.
4. Sharon, N. *Pure Appl. Chem.* **1988**, *60,* 1389-1394.
5. Fuentes, J.; Moreda, W.; Ortiz, C.; Robina, I. and Welsh, C. *Tetrahedron* **1992**, *48*, 6413-6424.
6. Fuentes Mota, J.; Pradera Adrián, M. A.; Ortiz Mellet, C. and García Fernández, J. M. *Carbohydr. Res.* **1986**, *153*, 318-324.
7. Khodin, A. Ya.; Zurabyan, S. E. and Macharadze, R. G., *Carbohydr. Res*. **1980**, *85*, 201-208.
8. Garg, H. G. and Jeanloz, R. W. Synthetic *N*- and *O*- Glycosyl Derivatives of L-Asparagine, L-Serine, and L-Threonine. In *Adv. Carbohydr. Chem. Biochem.*, Tipson, R. S., Horton, D; Eds.; Academic Press: New York, 1985; Vol. 43, 135-201.
9. Günther, W. and Kunz, H., *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1050-1051.
10. Mukeree A. K. and Ashare, R., *Chem. Rev.* **1991**, *91*, 1-24.
11. Avalos, M.; Babiano, R.; Garcla-Verdugo, C.; Jiménez, J. L.; Palacios, J. C., *Tetrahedron Lett.* **1990**, *31*, 2467-2470.
12. Witczak, Z., *Tetrahedron Lett.* **1986**, *27*, 155-158.
13. Hassel, T. and Müller, H. P., *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 359-360.
14. Nguyen Dinh Thanh, Nguyen Thi Thanh Mai, *Carbohydr. Res.*, **2009**, 344, 2399-2405.
15. Nguyen Dinh Thanh, Pham Hong Lan, Dang Nhu Tai, *Journal of Chemistry (VAST)* **2008**, *46*, 427-431.
16. Nguyen Dinh Thanh, Dang Nhu Tai, Duong Thu Nguyet, *Journal of Science, Natural Sciences and Technology, Vietnam National University (Hanoi),* **2006**, *XXII*, 174-178.
17. Nguyen Dinh Thanh, Dang Nhu Tai, Bui Thi Thu Trang, *Journal of Science, Natural Sciences and Technology, Vietnam National University (Hanoi),***2006**, *XXII*, 179-183.
18. Lemieux, R. U., *Methods Carbohydr. Chem.* **1963**, *2*, 221-222.
19. Teiichi Murakami, Reiko Hirono, Yukari Sato, Kiyotaka Furusawa, *Carbohydr. Res.* **2007**, *342,* 1009-1020.
20. Hogg, A.M.; Nagabhushan, T.L., *Tetrahedron Lett.* **1972***, 13,* 4827-4830;
21. Yang, L. P.; Li, S. Z.; Li, Y. C.; Gao, R. Y., *Chin*. *J*. *Pestic*. *Sci*. **2002,** *4*, 67-70.