SYNTHESIS OF 2-AMINOTHIAZOLIDIN-4-ONES FROM (HEPTA-*O*-ACETYL-β-MALTOSYL)THIOSEMICARBAZONES OF SUBSTITUTED ACETOPHENONES

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Abstract. Reaction of substituted acetophenone (hepta-*O*-acetyl-β-maltosyl)thiosemicarbazones with ethyl bromoacetate was investigated. It's indicated that the nature of solvents and the catalysts affected the reaction yields, and that the microwave-assisted heating method gave higher yields of products than the conventional heating one. Based on the optimum conditions, ionic liquid [HOCH$_2$CH$_2$NH$_3^+$]$^-$OAc, dried chloroform and microwave-assisted heating, the synthesis of some 2-iminothiazolidin-4-ones containg maltose moiety were synthesized. Their structure have been confirmed by spectral data (FTIR, ^{1}H NMR, ^{13}C NMR and MS).

Keywords: Ionic liquid, 2-Iminothiazolidin-4-one, β-Maltose, Microwave-assisted, Thiosemicarbazones

4-Thiazolidinone derivatives constitute an important class of heterocyclic compounds for their potential pharmaceutical applications, and they were interested to synthesize. The presence of thiazolidinone moiety in the structure of several naturally occurring molecules with important antibiotic, immunosuppressive and antitumor activities has been known for several years [1–4]. The aminothiazole ring system has found application in drug development for the treatment of HIV-infection, hypertension and inflammation [5]. Several thiazolidinone derivatives have been shownto exhibit excellent bactericidal [6], fungicidal [7], anthelmintic [8], anti-HIV [9] activities.

Reaction of substituted acetophenone hepta-*O*-acetyl-β-maltosyl thiosemicarbazones with ethyl bromoacetate carried out below (Scheme 1). The influences of base catalyst and the nature of solvents to reaction, which took place between substituted acetophenone hepta-*O*-acetyl-β-matosylthiosemicarbazones and ethyl bromoacetate, were investigated. Base Lewis' catalysts

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and solvents, also obtained results were represented in Table 1. Acetophenone hepta-*O*-acetyl-β-matosylthiosemicarbazone **1g** was used in this investigation.
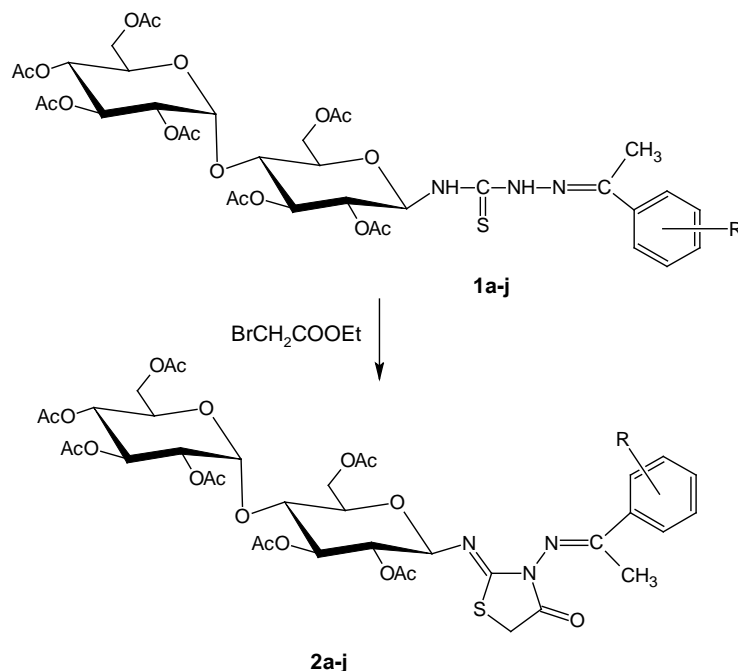
R=4-NO$_2$ (**a**), 3-NO$_2$ (**b**), 4-Cl-3-NO$_2$ (**c**), 4-CH$_3$-3-NO$_2$ (d), 4-Cl (**e**), 4-Br (**f**), H (**g**), 4-CH$_3$ (**h**), 4-OH (i), 4-OCH$_3$ (**j**)

Scheme 1. Conversion of acetophenone hepta-*O*-acetyl-β-maltosyl thiosemicarbazones.

From Table 1, it's shown that the reaction of thiosemicarbazones **1g** with ethyl bromoacetate did not occurred when tertiry amines, such as triethylamine and DABCO, were used in any solvent that was chosen, such as ethanol, toluene, dichloromethane, chloroform, even if reaction time was extended until 12–16 h. This reaction was only occurred with good yields when sodium acetate was used as catalyst. In these cases, reaction time and yield of 2-iminothiazolidin-4-one **2g** also were changed according to the nature of solvents. For example, when solvent was absolute ethanol, then reaction time was 12 h, but a apolar solvent, such as (anhydrous) toluene, was used, then reaction time shortened to 8 h. The use of aprotic polar solvents, such as (anhydrous) chloroform or dichloromethane, made reaction time to shorten remarkably, simultaneously, the yield of 2-iminothiazolidin-4-one **2g** was significantly increased. We realized that the performance of this reaction in anhydrous chloroform gave the higher yield obtained (67%) in the shorter reaction time (6 h). The use of microwave-assisted synthetic method in this case gave the highest yield of **2g** (88%) in the shortest reaction time (40 min *vs.* 6 h), and of ionic liquid named 2-hydroxyethylammonium acetate,

[HOCH$_2$CH$_2$NH$_3^+$]$^-$OAc, with yield of 90% for 20 min. The change of reaction time and yield of **2g** in case of the use of anhydrous sodium acetate as catalyst could be summaried as follows:

Table 1. Investigation of influences of solvents and catalysts to reaction between thiosemicarbazon **2g** and ethyl bromoacetate

Solvent	Catalyst	Reaction time (h)	Yield, %	Solvent	Catalyst	Reaction time (h)	Yield, %
CHCl$_3$	CH$_3$COONa	6	67	CH$_2$Cl$_2$	DABCO	12	Not formed
CHCl$_3$	CH$_3$COONa	40 min (MW oven)	88	Toluene	NaCOOCH$_3$	8	42
CHCl$_3$	**[HOCH$_2$CH$_2$NH$_3^+$]$^-$OAc**	**20 min (MW oven)**	**90**	Toluene	NaCOOCH$_3$	8	42
CHCl$_3$	NEt$_3$	12	Not formed	Toluene	NEt$_3$	12	Not formed
CHCl$_3$	DABCO	12		Toluene	DABCO	12	Not formed
CH$_2$Cl$_2$	NaCOOCH$_3$	8	47	Ethanol	NaCOOCH$_3$	12	38%
CH$_2$Cl$_2$	NEt$_3$	12	Not formed	Ethanol	NEt$_3$	12	Not formed
				Ethanol	DABCO	16	Not formed

Reaction time: CHCl$_3$ > CH$_2$Cl$_2$ ≈ toluene > ethanol

Yield: CHCl$_3$ > CH$_2$Cl$_2$ > toluene > ethanol

Based on the obtained above results, other 2-iminothiazolidin-4-one **2a-j** with different substituents were synthesized using the optimum investigated conditions ([HOCH$_2$CH$_2$NH$_3^+$]$^-$OAc, anhydrous chloroform and microwave-assisted heating, Table 2). Reaction yields were relative high, from 56% to 91%. 2-Iminothiazolidin-4-ones **2** were white or pale yellows solids, having high melting points, and soluble in organic solvents 2-Iminothiazolidin-4-ones **2**(such as ethanol, methanol, dichloromethane, chloroform, toluene, benzene, ethyl acetate, acetone). The ^{1}H NMR (and ^{31}C NMR) spectral data showed that obtained products were isomeric mixture. We realized that these isomers couldn't seperated out

by using chromatographic method. The ratios of 2-iminothiazolidin-4-ones **2** and **2'** could be obtained from ^{1}H NMR (Table 2).

Table 2. 2-Iminothiazolidin-4-ones **2** from substituted acetophenone (hepta-*O*-acetyl-*β*-maltosyl)thiosemicarbazones **1**

Entry	R	mp (ºC)	Yield %	Ratio of 2, %	IR Spectra (cm^{-1})			
					$\nu_{C=N}$	$\nu_{C=O}$	ν_{COC}	**Other** ν
2a	4-NO$_2$	145–147	89	86/14	1602	1760	1218, 1071	1590,1523,1455
2b	3-NO$_2$	116–118	89	~100/0	1627	1749	1230, 1051	1590,1560,1520
2c	4-Cl-3-NO$_2$	175–177	75	57/43	1614	1745	1233, 1051	1578,1540
2d	4-CH$_3$-3-NO$_2$	170–172	77	~100/0	1615	1749	1224, 1048	1590,1532,1500
2e	4-Cl	190–192	90	73/27	1613	1744	1236, 1048	1582,1490
2f	4-Br	168–170	91	~100/0	1627	1752	1226; 1034	1590,1490
2g	H	177–179	88	70/30	1619	1762,1735	1250,1229,1070	1585,1500,1439
2h	4-CH$_3$	160–162	81	100/0	1615	1753	1231; 1049	1590,1510
2i	4-OH	158–160	56	~100/0	1614	1744	1244, 1032	1510,1480
2j	4-OCH$_3$	139–141	90	☐100/0	1611	1750	1227, 1050	1514,1490

The formation of 2-iminothiazolidin-4-ones **2** could be preliminarily confirmed by using IR spectroscopic method. In spectra of 2-iminothiazolidin-4-ones **2**, the disappearance of absorption band at 1602–1622 cm^{-1}, which is characteristic for imine bond C=N, and apprearance of absorption band at 1613–1627 cm^{-1}, which is characteristic for C=O bond of lactam. Other absorption bands which belong to acetate group and benzene ring, in general, were only shifted insignificantly. From ^{1}H NMR spectra, we found that reaction of thiosemicarbazones **1b**, **1d**, **1f**, **1h**, **1i** and **1j** with ethyl bromoacetate gave unique product **2** formed (that's **2b**, **2d**, **2f**, **2h**, **2i** and **2j**), whereas in remained cases, for thiosemicarbazones **1a**, **1c**, **1e** and **1g**, the mixture of two isomers was obtained. Ratios of these isomers were changed

Table 3. ^{1}H NMR Spectra of 2-iminothiazolidin-4-ones (**2a-j**) from acetophenone hepta-*O*-acetyl-β-

maltosylthiosemicarbazones **1**

R	4-NO₂	3-NO₂	4-Cl-3-NO₂	4-CH₃-3-NO₂	4-Cl	4-Br	H	4-CH₃	4-OH	4-OCH₃
Proton	**2a**	**2b**	**2c**	**2e**	**2f**	**2g**	**2h**	**2j**	**2l**	**2m**
CH₃C=N	2.38,s	2.53,s	2.46,s	2.56,s	2.44,s	2.44,s	2.46,s	2.43,s	2.39,s	2.46,s
H-2'''	8.12,d,9.0	8.64,t,2.0	8.45,s	8.33,s	7.88,d,8.5	7.66,d,8.5	7.88–7.86,m	7.77,d,8.0	7.73,d,8.5	7.84,d,9.0
H-3'''	8.30,d,9.0	-	-	-	7.52,d,8.5	7.81,d,8.5	7.46–7.45,m	7.26,d,8.0	6.82,d,8.5	7.00,d,9.0
H-4'''	-	8.29,t,8.0, 1.25	-	-	-	-	7.46–7.45,m	-	-	-
H-5'''	8.30,d,9.0	7.76,t,8.0	7.87,d,8.5	7.60,d,8.25	7.52,d,8.5	7.81,d,8.5	7.46–7.45,m	7.26,d,8.0	6.82,d,8.5	7.00,d,9.0
H-6'''	8.12,d,9.0	8.30,d,8.0	8.15,d,8.5	8.09,d,8.25	7.88,d,8.5	7.66,d,8.5	7.88–7.86,m	7.77,d,8.0	7.73,d,8.5	7.84,d,9.0
H-1'	6.13,m	6.14,m	6.11, m	6.14,m	6.14,m	6.14,m	6.16,m	6.15,m	6.15,m	6.15,m
H-1"	5.38,d,3.5	5.38,d,3.0	5.38,d,3.0	5.22,d,3.0	5.38,d,3.0	5.38,d,3.0	5.38,d,3.5	5.38,d,3.5	5.38,d,4.0	5.38,d,3.5
H-2'	5.89,m	5.88,m	5.72, m	5.72,m	5.87,m	5.87,m	5.86,m	5.87,m	5.85,m	5.85,m
H-3"	5.56,t,9.25	5.56,t,9.25	5.55,t,9.25	5.49,d,9.0	5.55,t,9.25	5.55,t,9.25	5.55,t,9.25	5.55,t,9.25	5.53,t,9.25	5.54,t,9.25
H-3'	5.25,t,10.0	5.25,t,10.0	5.25,m	5.24,dd,17.0, 9.5	5.24,t,10.0	5.24,t,10.0	5.25,t,10.0	5.25,t,10.0	5.24,t,10.0	5.25,t,10.5
H-2"	4.99,t,10.0	5.00,t,9.75	5.00,m	5.00,t,10.0	5.00,t,9.5	5.00,t,9.75	5.00,t,9.5	5.00,t,9.75	5.00,t,9.75	5.00,t,9.75
H-5"	4.89,dd,10.5,3.5	4.89,dd,10.5,3.5	4.87,m	4.86,dd,13.0, 3.0	4.89,t,10.5	4.89,dd,10.5,3.5	4.88,dd,10.0,3.5	4.88,dd,10.5,3.5	4.88,dd,10.5,3.5	4.88,dd,10.5,3.75
H-4"	4.44,d,12.0	4.45,d,11.5	4.42,m	4.41,d,11.5	4.43,t,13.5	4.44,d,12.0	4.43,d,13.75	4.44,d,11.5	4.44,d,12.0	4.44,d,11.5
H-5'	4.29–4.26,m	4.19–4.13,m	4.26,m	4.26,m	4.26–4.25,m	4.28–4.24,m	4.27–4.25,m	4.27–4.24,m	4.26–4.23,m	4.27–4.24,m
H-6'a	4.21–4.16,m	4.19–4.13,m	4.18–4.11,m	4.16,dd,12.5, 4.5	4.18–4.11	4.17,dd,12.0,4.0	4.18–4.11,m	4.17,dd,12.25,4.25	4.16,dd,12.0,4.5	4.16,dd,12.0,4.5
H-6"a	4.21–4.16,m	4.19–4.13,m	4.18–4.11,m	4.12,dd,13.0, 4.75	4.18–4.11	4.13,dd,12.5,4.5	4.18–4.11,m	4.13,dd,12.25,4.75	4.12,dd,12.5,5.0	4.13,dd,12.5,4.5

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R	4-NO₂	3-NO₂	4-Cl-3-NO₂	4-CH₃-3-NO₂	4-Cl	4-Br	H	4-CH₃	4-OH	4-OCH₃
Proton	**2a**	**2b**	**2c**	**2e**	**2f**	**2g**	**2h**	**2j**	**2l**	**2m**
H-6"b	4.12–4.09,m	4.09–3.94,m	4.10–4.02,m	4.08–3.98,m	4.10–4.01,m	4.06–3.93,m	4.04–3.90,m	4.04–3.92,m	4.03–3.90,m	4.03–3.93,m
H-6'b	4.12–4.09,m	4.09–3.94,m	4.10–4.02,m	4.08–3.98,m	4.10–4.01,m	4.06–3.93,m	4.04–3.90,m	4.04–3.92,m	4.03–3.90,m	4.03–3.93,m
H-5a	4.29–4.26,m	4.09–3.94,m	4.10–4.02,m	4.08–3.98,m	4.10–4.01,m	4.06–3.93,m	4.04–3.90,m	4.04–3.92,m	4.03–3.90,m	4.03–3.93,m
H-5b	4.29–4.26,m	4.09–3.94,m	4.10–4.02,m	4.08–3.98,m	4.10–4.01,m	4.06–3.93,m	4.04–3.90,m	4.04–3.92,m	4.03–3.90,m	4.03–3.93,m
H-4'	3.97,t,9.25	3.97,t,9.25	3.98,t,9.5	3.83,t,9.5	4.10–4.01,m	4.06–3.93,m	3.83,t,9.5	4.04–3.92,m	4.03–3.90,m	4.03–3.93,m
CO*CH₃*	2.05–1.93	2.05–1.93	2.03–1.89	2.09–1.96	2.03–1.89	2.03–1.88	2.03–1.89	2.03–1.89	2.07–1.88	2.01–1.83
Other proton				2.46,s,**4-CH₃**				2.35,**4-CH₃**	9.86,**4-OH**	3.81,**4-OCH₃**

Table 4. ¹³C NMR Spectra of 2-iminothiazolidin-4-ones (**2a-j**) from acetophenone hepta-*O*-acetyl-*β*-maltosylthiosemicarbazones **1**

R	4-NO₂	3-NO₂	4-Cl-3-NO₂	4-CH₃-3-NO₂	4-Cl	4-Br	H	4-CH₃	4-OH	4-OCH₃
Carbon	**2a**	**2b**	**2c**	**2e**	**2f**	**2g**	**2h**	**2j**	**2l**	**2m**
C=O(lactam)	171.4	171.5	170.0	170.5	171.5	171.5	171.5	171.6	171.5	171.6
CO*CH₃*	169.9–169.1	170.0–169.1	169.9–169.1	169.9–169.1	169.9–169.1	169.9–169.1	169.9–169.0	169.9–169.0	169.9–168.9	169.9–168.9
C-2	160.7	160.8	160.5	160.3	160.5	161.5	162.4	162.3	162.0	162.0
C=N imine	127.7	130.1	131.8	130.7	128.2	131.4	128.4	129.0.	128.3	128.1
C-1'''	148.2	148.0	137.6	141.9	134.9	136.5	137.4	139.9	148.2	129.8
C-2'''	127.7	132.9	123.2	121.9	128.3	128.5	128.4	126.5	128.3	128.1
C-3'''	123.6	132.9	147.7	149.1	128.5	131.4	126.5	129.0	115.2	113.8

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R	4-NO$_2$	3-NO$_2$	4-Cl-3-NO$_2$	4-CH$_3$-3-NO$_2$	4-Cl	4-Br	H	4-CH$_3$	4-OH	4-OCH$_3$
Carbon	2a	2b	2c	2e	2f	2g	2h	2j	2l	2m
C-4'''	143.4	124.4	131.3	136.6	136.2	123.7	130.1	134.7	159.5	160.9
C-5'''	123.6	120.8	131.2	133.0	128.5	131.4	126.5	129.0	115.2	113.8
C-6'''	127.7	138.9	131.8	134.3	128.3	128.5	128.4	126.5	128.3	128.1
C-1''	95.3	95.3	95.3	95.3	95.3	95.3	95.3	95.3	95.3	95.3
C-1'	79.3	79.3	82.3	82.4	82.4	79.2	77.0	82.4	79.2	79.2
C-4'	74.8	74.8	76.9	76.9	76.9	74.8	74.8	76.9	74.8	74.9
C-5'	73.4	73.4	74.7	74.7	74.8	73.4	73.7	73.7	73.4	73.6
C-5''	73.2	73.2	73.7	73.7	73.7	73.2	73.2	73.2	73.3	73.4
C-3'	69.5	69.5	73.2	73.2	73.2	69.5	69.5	69.5	69.5	69.5
C-3''	68.9	68.9	69.5	69.5	69.5	68.9	68.9	68.9	68.9	68.9
C-2''	68.1	68.1	68.8	68.9	68.9	68.0	68.1	68.0	68.1	68.1
C-4''	67.7	67.7	68.0	68.0	68.0	67.7	68.0	67.8	67.8	67.7
C-2'	67.5	67.5	67.8	67.8	67.8	67.5	67.8	66.0	67.5	67.6
C-6''	62.6	62.6	62.7	62.7	62.6	62.5	62.6	62.5	62.6	62.6
C-6'	61.7	61.4	61.4	61.4	61.4	61.4	61.3	61.7	61.7	61.7
C-5	31.8	31.7	31.8	31.7	31.7	31.6	31.6	31.6	31.5	31.5
COCH$_3$	20.5–20.2	20.5–20.2	20.5–20.2	20.9–20.2	20.9–20.2	20.5–20.2	20.9–20.2	20.8–20.2	20.9–20.2	20.5–20.2
C=N–CH$_3$	15.0	14.9	14.7	14.7	14.8	14.7	14.9	14.8	14.7	14.7
Other carbon				19.3,4-CH$_3$				20.8,4-CH$_3$		55.2,4-OCH$_3$

Table 5. ESI-MS of 2-iminothiazolidin-4-ones from acetophenon hepta-O-acetyl-β-maltosylthiosemicarbazones (**2 a-j**)

Entry	R	M (calcd., Da)	[M]+	[M+H]+ found,% (calcd.)	[M+Na]+ found,% (calcd.)
2a	4-NO$_2$	896.23	-	897.11, *12* (897.23)	919.24, *100* (919.22)
2b	3-NO$_2$	896.23	-	897.34, *6.5* (897.23)	919.38, *100* (919.22)
2c	4-Cl-3-NO$_2$	930.19/932.19	-	-	953.09, *100*/955.02, *47* (953.18/955.17)
2e	4-CH$_3$-3-NO$_2$	910.24	-	-	933.21, *20* (933.23)
2f	4-Cl	885.20/887.20	-	886.02, *100*/888.02, *43* (886.21/888.21)	-
2g	4-Br	929.15/931.15	-	930.16, *97* /932.09, *100* (930.16/932.16)	954.10, *4*/954.09, *3.5* (952.14/954.14)
2h	H	851.24	-	852.27, *100* (852.25)	874.22, *85* (874.23)
2j	4-CH$_3$	865.26		866.59, *100* (866.26)	888.25, *49* (888.25)
2l	4-OH	867.24	-	868.38, *36* (868.24)	890.35, *100* (890.23)
2m	4-OCH$_3$	881.25	-	882.34, *19* (882.26)	904.33, *100* (904.24)

Note: -The values in parentheses are theorical ones.

independing on the nature of substituent on benzene ring, for example, ratio of **2** was 80:11 (%) for 4-NO$_2$ group, whereas the one was 57:13 (%) for 4-Cl-3-NO$_2$, and essentially, isomer **2** always predominated over. IR spectra show the characteristic absorption bands at 1753–1744 cm^{-1} ($v_{C=O}$ ester), 1627–1613 cm^{-1} ($v_{C=O}$ lactam), 1590–1480 cm^{-1} ($v_{C=C}$), 1242–1226 and 1051–1034 cm^{-1} (v_{COC} ester). The evidences that confirm the success of reactions are the absence chemical shifts at δ 10.7–10.9 ppm (singlet, NH) and δ 8.5–8.6 ppm (doublet, NH) (in ^{1}H NMR spectra). Other evidence is the disappearance of C=S signals at at δ 179.4–179.3 ppm, and the appearance of C=O (lactam) signals at δ 171.6–171.0 ppm (in ^{13}C NMR spectra). The ^{1}H NMR and ^{13}C NMR spectral elucidations of these products indicated the presence of two isomers in each obtained product. Tables 3 and 4 showed ^{1}H NMR and ^{13}C NMR spectral data for only isomer **2a-j**, the ones for isomer **2'a-j** will be discussed in our other paper. ESI-MS spectra of 2-iminothiazolidin-4-ones **2** had molecular peaks, often [M+H]+ or [M+Na]+ peaks, with high intensity, and in general were base peaks (Table 3).

In brief, spectral data (IR, ^{1}H NMR, ^{13}C NMR and ESI-MS) confirmed the structures of 2-iminothiazolidin-4-ones synthesized from substituted acetophenone hepta-*O*-acetyl-*β*-maltosylthiosemicarbazones.

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. Substituted acetophenone hepta-*O*-acetyl-β-D-maltosyl thiosemicarbazones **1** were synthesized by method described in previous paper [10].

General procedure for conversion of substituted acetophenone tetra-O-acetyl-β-D-glucopyranosyl thiosemicarbazones (**1**) *into 2-iminothiazolidin-4-one compounds* (**2**). To a suspension mixture of per-*O*-acetyl-β-maltosyl thiosemicarbazone **1** (2.5 mmol) and $[HOCH_2CH_2NH_3^+]^-OAc$ (0.05 mL) in dried chloroform (35 mL) was added ethyl bromoacetate (0.42 mL). Reaction mixture was heated with reflux for 40 min in MW oven. The solvent was removed under reduced pressure, the residue was washed with n-hexane for removing ethyl bromoacetate, and with water (2-3 times) for removing sodium acetate. The obtained solid was recrystallized from 95% ethanol to afford the title compounds **2** or **2'**.

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