ISATIN (PER-*O*-ACETYL-β-D-GALACTOPYRANOSYL)THIOSEMICARBAZONES

Nguyen Dinh Thanh*, Nguyen Thi Kim Giang
Faculty of Chemistry, College of Science, Vietnam National University (Hanoi), 19 Le Thanh Tong, Hanoi (Vietnam)

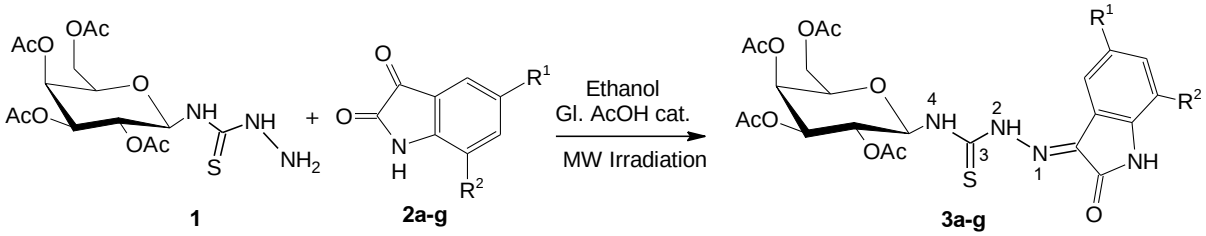
Abstract. Some novel substituted isatin (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)thiosemicarbazones were synthesized by reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl thiosemicarbazide with these isatins. The reaction was carried out by using microwave-assisted heating method.

Introduction

The derivatives of isatins have remarkable biological activities, such as anticonvulsant [1], anti-HIV [2], cytotoxic, [3] tuberculostatic [4], anti-microbial [5]. Numerous thiosemicarbazone compounds containing isatin component have been synthesized. We have carried out to study on syntheses and transformations of thiosemicarbazones from substituted isatins and peracetylated glycopyranosyl thiosemicarbazides [6]. We reported herein the synthesis of substituted isatin (tetra-*O*-acetyl-β-D-galactopyranosyl)thiosemicarbazones from 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl thiosemicarbazide. Required 5- and 7-Substituted isatins (**2a-g**) were prepared using clasical Sanmayer's reaction from corresponding substituted anilines or by directly bromation or nitration of isatin **2e** ($R^1 = R^2 = H$).

Results and discussion

(Tetra-*O*-acetyl-β-D-galactopyranosyl)thiosemicarbazone derivatives (**3a-g**) of above isatins were synthesized by reaction of the latter compounds with tetra-*O*-acetyl-β-D-galactopyranosyl thiosemicarbazide **1**. The reaction was carried out in absolute ethanol in the presence of glacial acetic acid as catalyst using microwave-assisted heating method. Irradiation time was at interval of 5–7 min in 600 W-microwave power. The reaction mixture became clear after irradiation time for 50–60 s and the product's precipitate ready appeared when reaction mixture was cooled to room temperature.



1 **2a-g** **3a-g**

Scheme 1. Synthetic pathway for isatin (2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)thiosemicarbazones **3a-g**.

The yields of thiosemicarbazones **3a-g** were 56–90%. These compounds were soluble in common organic solvents, such as ethanol, methanol, toluen, DMF, DMSO,

aceton,… but insoluble in water. They have yellow chrome or orange red colors, and high melting temperatures (Table 1).

IR spectra of isatin (2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)-thiosemicarbazones showed absorption bands in region at 3343–3207 cm^{-1}, which belong to stretching vibration of –NH group. Intensive absorption bands at 1754–1747, 1230–1219 and 1084–1040 cm^{-1} belonged to carbonyl group in ester function of monosarcazide moiety. Stretching vibration of C=S bond had medium intensive band at 1389–1346 cm^{-1}. Imine bond have absorption band at 1632–1611 cm^{-1} (Table 1).

Table 1. Substituted isatin (2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)thiosemicacbazones (**3a-g**)

Entry	R^1,R^2	mp (°C)	Yield (%)	Reaction time (min)	IR (cm^{-1})					Mass spectra
					ν_{NH}	$\nu_{C=O}$	ν_{C-O-C}; ν_{C-O-C}	$\nu_{C=S}$	$\nu_{C=N}$	[M-H]
3a	5,7-diBr	209-211	73	3	3213	1750	1230; 1050	1377	1611	
3b	5-NO_2	165-166	85	3	3207	1754	1224; 1043	1346	1632	594.12
3c	5-Br	156-158	74	4	3349	1750	1229; 1049	1370	1615	627.13/ 629.11
3d	5-Cl	145-147	90	3	3341	1751	1219. 1046	1358	1624	585.00
3e	H	176-179	88	5	3385	1752	1225; 1040	1389	1621	549.23
3f	7-CH_3	225-227	56	6	3284	1747	1223; 1056	1373	1627	565.44*
3g	5-*i*-C_3H_7	150-152	86	7	3343	1748	1221; 1084	1373	1629	591.11

* $[M+H]^+$

^{1}H-NMR spectra of these thiosemicarbazones showed that protons in sugar moiety had chemical shifts in regions at δ = 4–6 ppm. Aromatic protons showed signals at δ = 7–8 ppm. The chemical shifts of the NH(2) and NH(4) protons are observed at δ = 12.84–12.56 ppm (singlet) and δ = 10.05–9.55 ppm (doublet) with coupling constants *J* = 9.0 Hz. The anomeric configuration of the pyranose rings in these thiosemicarbazones is clearly established by ^{1}H NMR spectroscopy. The β anomeric D-galactose unit shows a characteristic signal for H-1 (^3J= 9.0–9.5 Hz), which is consistent with the 1,2-trans relationships between protons H-1' and H-2' (Tables 2 and 3). Carbon atoms in isatin component of these thiosemicarbazones showed signals at δ = 119–131 ppm in their ^{13}C NMR spectra. Imine carbon atom had chemical shift at δ = 142–144 ppm. The position of this signal depended on substituent's nature on benzene ring of isatin component. Carbon atom in thione bond C=S gave signal at 179.5–179.0 ppm (Table 4).

Table 2. [1]H-NMR Spectral data of some substituted isatin (2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)thiosemicarbazones (**3a-g**) [sugar moiety, δ (in ppm), *J* (in Hz)]

Entry	NH(4)		NH(2)	H-1		H-2	H-3	H-4	H-5		H-6		4×OCH_3
3a	9.68 (d)	*9.0*	12.56 (s)	5.95 (t)	*9.0*	5.24 (m)	5.34 (m)	5.15 (m)	4.31 (t)	*6.5*	4.07 (d)	*6.5*	2.11–1.91
3b	10.05 (d)	*9.0*	12.60 (s)	6.01 (t)	*9.0*	5.42 (m)	5.43 (m)	5.35 (m)	4.41 (t)	*6.5*	4.08 (d)	*6.5*	2.16–1.94
3c	9.79 (d)	*9.0*	12.63 (s)	5.98 (t)	*9.0*	5.37 (m)	5.40 (m)	5.34 (m)	4.40 (t)	*6.5*	4.07 (d)	*6.5*	2.16–1.94
3d	9.76 (d)	*9.0*	12.64 (s)	5.98 (t)	*9.0*	5.38 (m)	5.41 (m)	5.35 (m)	4.41 (t)	*6.0*	4.08 (d)	*6.0*	2.17–1.95
3e	9.62 (d)	*9.0*	12.77 (s)	5.94 (t)	*9.0*	5.39 (m)	5.42 (m)	5.34 (m)	4.38 (t)	*6.5*	4.04 (d)	*6.5*	2.15–1.94
3f	9.58 (d)	*9.0*	12.81 (s)	5.94 (t)	*9.0*	5.39 (m)	5.42 (m)	5.34 (m)	4.38 (t)	*6.5*	4.06 (d)	*6.5*	2.15–1.94
3g	9.55 (d)	*9.0*	12.84 (s)	5.94 (t)	*9.0*	5.41 (m)	5.43 (m)	5.35 (m)	4.39 (t)	*6.0*	4.07 (d)	*6.0*	2.17–1.95

Table 3. [1]H-NMR Spectral data of some substituted isatin (2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)thiosemicarbazones (**3a-g**) [isatin moiety, δ (in ppm), *J* (in Hz)]

Entry	H-1’	H-4’		H-5’		H-6’		H-7'	
3a	11.68 (s)	7.92 (s)	-	-	-	7.81 (s)	-	-	-
3b	11.85 (s)	8.68 (d)	*2.0*	-	-	8.29 (dd)	*8.5; 2.5*	7.12 (d)	*8.5*
3c	11.34 (s)	7.99 (s)		-	-	7.53 (dd)	*8.5; 2.0*	6.89 (d)	*8.5*
3d	11.24 (s)	7.88 (d)	*1.5*	-	-	7.41 (dd)	*8.0; 2.5*	6.95 (d)	*8.0*
3e	11.24 (s)	7.76 (d)	*7.5*	7.38 (t)	*8.0; 7.5*	7.12 (t)	*7.5; 7.5*	6.94 (d)	*8.0*
3f	11.30 (s)	7.59 (d)	7.5	7.03 (t)	7.5; 7.5	7.20 (d)	7.5	-	-
3g	11.17 (s)	7.61 (s)		-	-	7.26 (dd)	*8.0; 1.5*	6.85 (d)	*8.0*

* Other protons: **3f**, 2.22 (s, 3H, C***H₃***); **3g**, 2.89 (1H, C***H***$(CH_3)_2$); 1.23 - 1.22 (6H, CH(C***H₃***$)_2$)

Table 4. ^{13}C-NMR Spectral data of some substituted isatin (2,3,4,6-tetra-*O*-acetyl-*β*-D-galactopyranosyl)thiosemicarbazones (**3a-g**) [δ (ppm), J (Hz)]

Entry	C=S	4×CO (ester)	C1	C2	C3	C4	C5	C6	*C*H$_3$CO (ester)	C2'	C3'	C4'	C5'	C6'	C7'	C8'	C9'
3a	179.5	170.7 – 169.6	82.2	70.9	69.3	67.6	71.7	61.5	21.2 – 20.8	162.8	141.6	135.6	132.1	124.0	123.1	114.9	104.8
3b	179.1	170.0 - 169.3	82.5	70.8	68.6	67.5	72.0	61.4	20.5 - 20.3	162.9	147.7	142.7	131.3	127.3	120.8	116.9	111.3
3c	179.1	170.0 - 169.4	82.4	70.7	68.6	67.5	72.0	61.3	20.5 - 20.3	162.2	141.7	133.7	131.9	123.8	122.1	114.2	113.1
3d	179.1	170.0 - 169.3	82.3	70.7	68.6	67.5	72.0	61.3	20.5 - 20.3	162.3	141.3	132.0	130.8	126.6	121.6	121.1	112.6
3e	179.1	170.0 - 169.4	82.2	70.7	68.6	67.5	71.8	61.3	20.5 - 20.3	162.5	142.7	133.3	131.7	122.3	121.5	119.7	111.1
3f	179.1	170.0 – 169.4	82.2	70.7	68.6	67.5	71.8	61.3	20.5 – 20.3	163.0	141.3	133.7	132.9	122.3	120.6	119.4	118.9
3g	179.0	170.0 - 169.3	82.3	70.6	68.6	67.5	71.9	61.3	20.5 - 20.3	162.7	142.8	140.8	133.6	129.7	119.6	119.2	111.0

* Other carbon: **3f**, 15.8 (***C***H$_3$); **3g**, 33.2 (***C***H(CH$_3$)$_2$); 24.0 (CH(***C***H$_3$)$_2$)

In conclusion, we have reported a highly efficient method for the synthesis of tetra-*O*-acetyl-β-D-galactosyl)thiosemicarbazones of some substituted isatins using microwave-assisted heating conditions. The advantages in use of the latter method are shorter reaction times, high yields, and minimization of synthesis operations, solvent use, and waste generation.

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. Mass spectra were recorded on mass spectrometer LTQ Orbitrap XL^{TM} (ThermoScientific, USA) using ESI method.

General procedure for synthesis of substituted isatin (2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)thiosemicarbazones (**3a-g**): A suspension mixture of subtituted 2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl thiosemicarbazide **1** (2 mmol) and corresponding subtituted isatin **2a-g** (2 mmol) and glacial acetic acid (0.05 ml) in absolute ethanol (7 ml) was irradiated with refluxing for 3–7 min in microwave oven. After reaction the mixture was cooled to room temperature. The yellow or orange crytals were filtered with suction. The crude product was recrystallized from ethanol to afford the title substituted isatin (2,3,4,6-tetra-O-acetyl-β-D-galactopyranosyl)thiosemicarbazones **3a-g**.

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