ISATIN PER-*O*-GLUCOPYRANOSYL THIOSEMICARBAZONES

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Abstract. Several 5- and 7-substituted isatins were prepared from corresponding anilines or unsubstituted isatin. Some novel substituted isatin (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazones (**3a-g**) 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

Thiosemicarbazone derivatives of saccharides[1] is interested because they showed significantly biological activities, such as antimicrobial, anti-inflammatory, antioxidant, ect…[2] In the other hand, isatin (indol-2,3-dione) is a resourceful endogenous heterocyclic molecule identified in human being and rat tissues.[3] Several of its derivatives were reported to exhibit a wide range of promising pharmacodynamic profile like anticonvulsant,[4] anti-HIV,[5] cytotoxic,[6] tuberculostatic,[7] anti-microbial.[8] At milimolar concentrations isatin has been found to inhibit different enzymes, an effect that may contribute to its anti infective actions.[9] Isatin has been preferred because during initial screening it has shown activity in the MES test.[10]

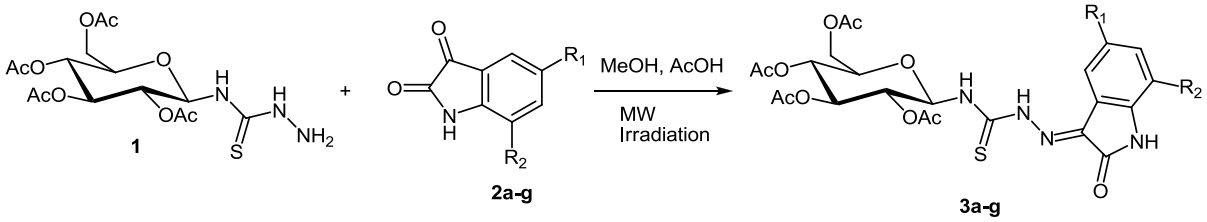
In intent to find some new bioactive compounds containing isatin component, we have carried out to study on syntheses and transformations of thiosemicarbazones from substituted isatins and peracetylated glucopyranosyl thiosemicarbazides. Based on these findings, we describe the synthesis of some compounds featuring monosaccharide moiety fused onto the isatin moiety with the aim of obtaining more potent pharmacologically active compounds. We reported herein the preparation of substituted isatin (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazones **3a-g** using microwave-assisted method.

Results and discussion

The required isatin prescursors, 5- and 7-substituted isatins **2a-g**, were synthesized according to references.[12] The new substituted isatin (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-thiosemicarbazones (**3a-g**) were obtained by condensation of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl thiosemicarbazide (**1**)[13] with corresponding substituted isatins (**2a-g**) in the presence of glacial acetic acid as catalyst (Scheme 1). Per-*O*-acetylated β-D-glucopyranosyl thiosemicarbazide **1** were soluble in methanol and ethanol, but substituted isatin derivatives **3a-g** were hardly dissolved in these solvents, these derivatives only were soluble in heating. Therefore reaction reagents were dissolved in hot absolute methanol or ethanol and irradiated in domestic oven for 5–7 min. In the end of reaction process the precipitate appeared could be observed. Experimental results are given in Table 1.

IR spectra of thiosemicarbazones **3a-g** showed characteristic absorptions in the range of 3359–3335 and 3265–3167 cm^{-1} (N–H bond), 1751–1746, 1227–1216 and 1050-1037

cm^{-1} (ester), 1375–1372 cm^{-1} (C=S), and 1625–1616 cm^{-1} (C=N bond) (Table 1). The assignments of ^{1}H and ^{13}C were confirmed using HMBC and HSQC methods (for compound **3a**).



Scheme 1. Synthetic pathway of isatin (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-thiosemicarbazones **3a-g**; for groups R_3, R_4: see Tables 1.

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

Entry	R_3,R_4	Yield (%)	mp (°C)	Reaction time (min)	IR Spectral data (cm^{-1})					
					ν_{NH}	$\nu_{CH=N}$	$\nu_{C=O}$ este	ν_{COC} este	$\nu_{C=O}$ amit	$\nu_{C=S}$
3a	H,H	74	251–252	15	3335, 3265	1625	1750	1225, 1037	1731	1373
3b	Cl,H	52	202–203	10	3558, 3259	1619	1748	1227, 1043	1709	1375
3c	Br,H	59	197–198	10	3343, 3215	1624	1746	1216, 1050	1709	1372
3d	Br,Br	49	243–245	10	3359, 3167	1616	1748	1224, 1040	1688	1372
3e	NO_2,H	20	251–253	15	3632, 3102	1626	1751	1212, 1049	1710	1347
3f	Cl,NO_2	31	256-258	15	3365, 3101	1633	1742	1243, 1041	1710	1375
3g	Br,NO_2	35	260–261	8	3358, 3093	1627	1744	1229, 1040	1720	1373

The ^{1}H NMR spectra of the substituted isatin (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazones (**3a-g**) showed resonance signals in range at δ=5.91–3.98 ppm of glucopyranose ring and at δ=8.31–7.44 ppm of isatin ring. The β anomeric configuration of **3a-g** was confirmed on the basis of the coupling constant $J_{1,2}$=9.5 Hz in agreement with the 1,2-*trans*-diaxial relationships between protons H-1 and H-2 (Table 3). The ^{13}C NMR spectrum of compound **3a**, for example, showed resonance signals at δ 179.8 ppm (carbon atom in C=S group), δ 169.9–169.3 ppm (carbon atoms in C=O bond of acetyl groups), δ 152.7–120.7 ppm (isatin ring), 81.3–61.7 ppm (glucopyranose ring) and δ 21.1–21.5 ppm (methyl carbons in acetyl groups) (Table 2).

The assignments of ^{1}H and ^{13}C were confirmed using HMBC and HSQC methods (for compound **3a**). The long-range ^{13}C–^{1}H coupling are shown in HMBC spectrum, such as

between C=S and H-1, C4'a and H-7' and H-4', C-7'a and H-7', C-4' and H-7', ect… (Fig. 1, Table 2). The ^{1}H NMR spectra of the substituted isatin (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazones **3a-g** showed resonance signals in range at δ = 5.91–3.98 ppm of glucopyranose ring and at δ = 8.31–7.44 ppm of isatin ring. Protons in thiourea group show chemical shifts at δ = 12.77–12.44 ppm (NH-b, in singlet), and δ = 9.77–9.52 ppm (NH-a, in doublet) with coupling constant J = 9.0–9.5 Hz (Table 3). Proton in isatin component shows a sharp peak at δ = 11.99–11.21 ppm (in singlet). The β anomeric configuration of pyranose ring in compounds **3a-g** was confirmed on the basis of the coupling constant ^{3}J = 9.0–9.25 Hz in agreement with the 1,2-*trans*-diaxial relationships between protons H-1 and H-2 (Table 2, Fig. 2).

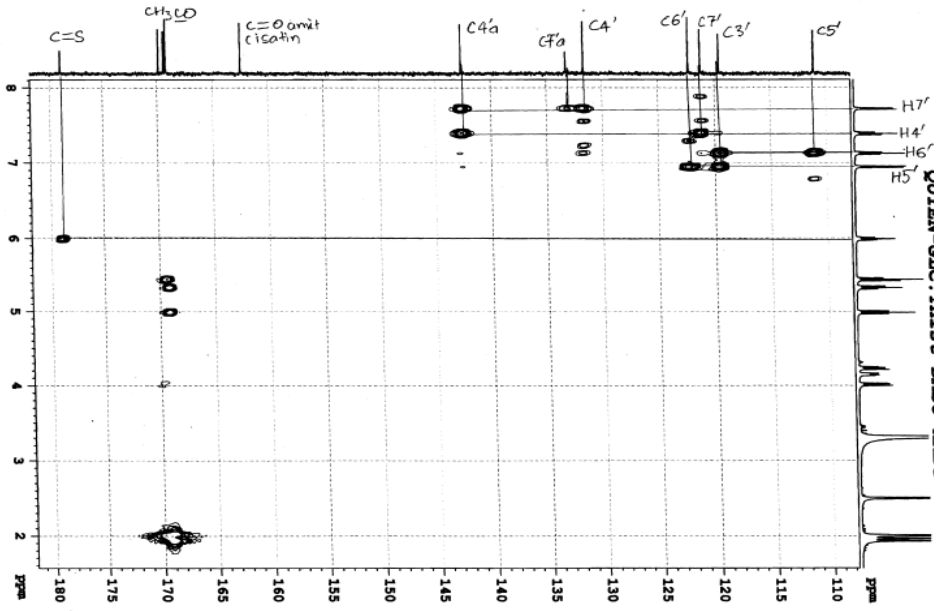


Figure 1. Partial HMBC spectrum of compound 3a.

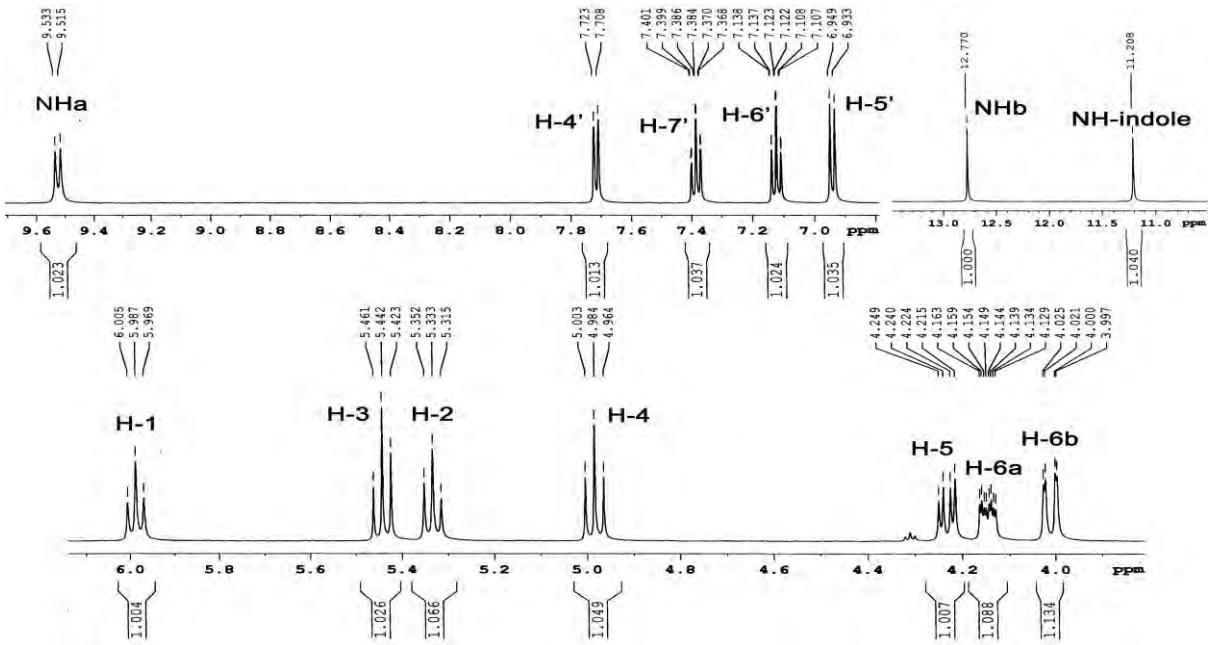


Figure 2. ^{1}H NMR spectrum of thiosemicarbazone 3a.

It's shown that the electronic nature of substituents affects the position of magnetic signals of protons [2-4]. This effect could be represented by Hammett's equations below for protons in groups CH-6' (A), NH_b (B) and NH-isatin (C), respectively:

$$\delta_{H\text{-}6'} = 1.15\ \sigma + 7.21\ (R^2 = 0.94) \qquad (A)$$

$$\delta_{NHb} = -0.26\ \sigma + 12.72\ (R^2 = 0.84) \qquad (B)$$

$$\delta_{NH\text{-}isatin} = 0.81\ \sigma + 11.19\ (R^2 = 0.97) \qquad (C)$$

Table 2. Selected summary in ^{1}H NMR spectra of compounds 3a-g

Proton	δ, ppm	Multiplicity	*J*, Hz
NH_b	12.77–12.44	s	
NH isatin	11.99–11.21	s	
NH_a	9.90–9.52	d	9.0–9.5
H-1	6.06–5.98	t	9.0–9.25
H-2	5.35–5.31	t	9.25
H-3	5.48–5.35	m or t	9.0–9.5
H-4	5.01–4.98	t	9.5–9.75
H-5	4.35–4.14	m, d or dq	9.5–10.0 (d) 9.5–10.0 and 2.0–2.5 (dq)
H-6a	4.25–4.24	t or dd	6.5 (t) 12.25–12.5 and 4.5–5.0 (dd)
H-6b	4.08–4.01	d or dd	11.0–11.5 (d) 11.0–12.5 and 1.5–1.7 (dd)
H-4'	8.27–7.72	s or d	1.5–7.5
H-5'	6.94	d	8.0
H-6'	8.34–7.12	s, d, dd or dt	1.5–2.25 (d) 8,5–7.5 and 1.5–2.5 (dd) 7.5 and 0.5 (dt)
H-7'	7.39–6.91	d or dt	8.0–9.0 (dd) 7.5 and 1.0 (dt)
4×CH_3CO	2.02–1.93	s	

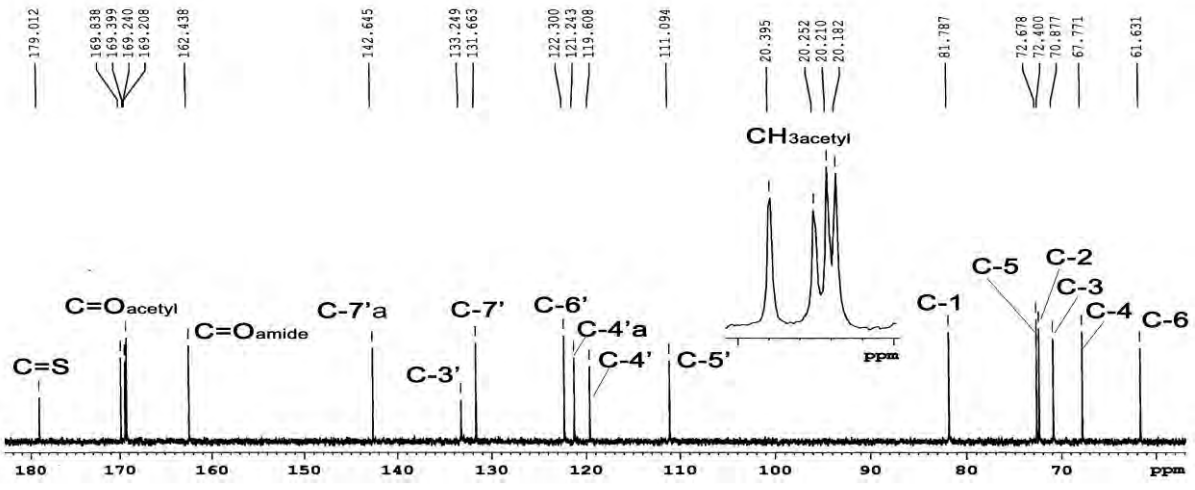


Figure 3. ^{13}C NMR spectrum of thiosemicarbazone **3a**.

In cases of (A) and (C), the values of parameter ρ are 1.15 and 0.81, respectively, it means that the withdrawing substituents (Hammett's σ > 0) caused resonance signals of these protons to shift downfield. Conversely, resonance signal of proton NH_b in thiourea functional group NHCSNH, which is nearby to imine group, shifts upfield (the parameter ρ has negative value. It means that there's an opposite influence of the substituents to resonance position in this case B [2-5].

The ^{13}C-NMR spectra of compound **3a-g** showed the main four-parted regions at δ = 179.09–178.01 ppm, 169.99–162.19 ppm, 81.97–61.13 ppm and 20.71–20.18 ppm. Signals at δ 179.09–178.01 ppm belonged to the carbon atom in the C=S group. The acetyl groups and carbonyl group of indole ring in these compounds showed resonance at δ = 169.99–162.19 ppm for carbonyl carbon atom and 20.71–20.18 ppm for the methyl carbon one. The presence of imine in molecule were confirmed by signal at δ 136.95–132.3 ppm, belong to imine carbon atom (Table 4, Fig. 3).

Table 3. Long-range ^{13}C–^{1}H interactions in HMBC spectrum of thiosemicarbazone 3**a**

Proton	δ_H (ppm)	HMBC
NH_b	12.77	179.01 (C=S); 133.25 (C-3')
NH isatin	11.21	162.44 (C=O amit);142.65 (C-7'a); 133.25 (C-3'); 119.61(C-4'a)
H-1	5.99	179.01 (C=S); 70.88 (C-2)
H-2	5.33	81.79 (C-1); 72.68 (C-3); 169.24 (*CO*CH_3)
H-3	5.44	70.88 (C-2); 67.77 (C-4); 169.40 (*CO*CH_3)
H-4	4.98	72.40 (C-5); 61.13 (C-6); 169.21 (*CO*CH_3)
H-6a	4.23	72.40 (C-5)
H-6b	4.01	72.40 (C-5); 67.77 (C-4); 169.84 (*CO*CH_3)
H-4'	7.72	142.65 (C-7'a); 133.25 (C-3'); 131.66 (C-7')
H-5'	6.94	122.30 (C-6'); 119.61 (C-4'a)
H-6'	7.12	119.61 (C-4'a); 111.09 (C-5')
H-7'	7.39	142.65 (C-7'a); 121.24 (C-4')

Table 4. Summary in ^{13}C NMR spectra of compounds **3a-g** *(δ in ppm)*

Carbon	δ, ppm	Carbon	δ, ppm
C=S	179.09–178.01	**C-1**	81.79–82.36
C-3'	136.95–131.45	**C-2**	71.00–68.64
C-4'	131.67–121.24	**C-3**	72.72–71.97
C-4a'	125.60–112.69	**C-4**	67.77–67.48
C-5'	142.76–111.09	**C-5**	72.50–72.40
C-6'	131.90–122.30	**C-6**	61.66–61.13
C-7'	132.32–111.30	**C=O amit**	162.60–162.19
C-7a'	147.73–126.07	**CH_3CO**	169.99–169.11
		***CH_3*CO**	20.53–18.49

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 methods for Synthesis of isatins(2,3,4,6-tetra-O-acetyl-β-D-glycopyranosyl)-thiosemicarbazones (**3a-g** and **4a-g**). A suspension mixture of (2,3,4,6-tetra-*O*-acetyl-β-D-glycopyranosyl)thiosemicarbazide **1** (1 mmol) and substituted isatin **2** (1 mmol) and glacial acetic acid (0.05 mL) in hot absolute methanol or ethanol (5 mL) was irradiated under reflux for 30 minutes in home-hold microwave oven. After irradiating for 15 minutes, the suspension mixture became clear solution. The irradiation was continued in given time. In the end of reaction, the precipitate was appeared. The reaction mixture was cooled to room temperature; the color precipitate was filtered with suction. The crude product was recrystallized from 95% ethanol or toluene: ethanol (1:1 in volume) to afford the title compounds of isatin (2,3,4,6-tetra-*O*-acetyl-β-D-glycopyranosyl) thiosemicarbazones[16].

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References and Notes

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