REACTION OF SOME SUBSTITUTED ISATIN WITH PER-*O*-ACETYL-β-D-GLUCOPYRANOSYL THIOSEMICARBAZIDE

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Abstract

Seven new substituted isatin (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazones were synthesized by reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl thiosemicarbazide and corresponding substituted isatin using microwave-assisted heating method.

1. INTRODUCTION

Thiosemicarbazone of saccharides [1] is interested because they showed significantly biological activities, such as antimicrobial, anti-inflammatory, antioxidant, etc… [2]. 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 previous papers, we have synthesized some peracetated glycopyranosyl thiosemicarbazides with several different aromatic carbonyl compound [11]. 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.

2. EXPERIMENTAL

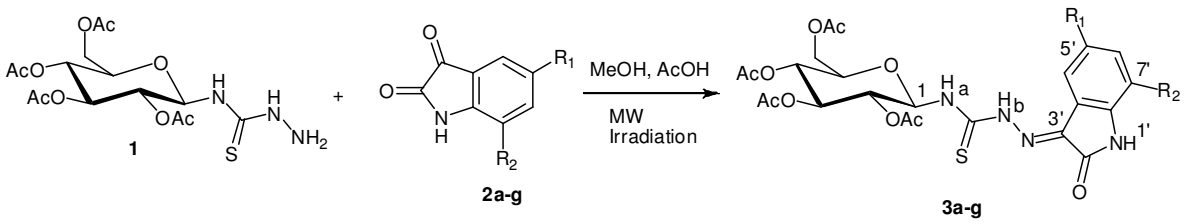
Melting points were determined on a STUART SMP3 apparatus (BIBBY STERILIN-UK). The IR spectra were recorded on a Magna 760 FT-IR Spectrometer (NICOLET, USA) in KBr disc. The ^{1}H-NMR (at 500.13 MHz) and ^{13}C-NMR (at 125.77 MHz) spectra were recorded on an AVANCE Spectrometer AV500 (BRUKER, Germany) in DMSO-d_6 solution in ppm compared to TMS as internal reference. (2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazide is prepared according to reference [11, 13b].

General methods for Synthesis of isatins(2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl)-thiosemicarbazones (**3a-g**). A suspension mixture of (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)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-glucopyranosyl) thiosemicarbazones.

3. RESULTS AND DISCUSSION

Required 5- and 7-substituted isatins **2a-g** were synthesized according to references [12]. Seven 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 was soluble in methanol and ethanol, but substituted isatin derivatives 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.



Scheme 1: Synthetic pathway of isatin (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazones **3a-g**

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

Entry	R_1,R_2	Yield (%)	mp (ºC)	$t_{reaction}$ (min)	IR Spectral data (cm^{-1})						ESIMS
					ν_{NH}	$\nu_{CH=N}$	$\nu_{C=O\ este}$	$\nu_{COC\ este}$	$\nu_{C=O\ amide}$	$\nu_{C=S}$	
3a	H,H	74	251–252	15	3335, 3265	1625	1750	1225, 1037	1731	1373	551.21*
3b	Cl,H	52	202-203	10	3558, 3259	1619	1748	1227, 1043	1709	1375	607.03/ 609.05
3c	Br,H	59	197-198	10	3343, 3215	1624	1746	1216, 1050	1709	1372	650.97/ 652.94
3d	Br,Br	49	243-245	10	3359, 3167	1616	1748	1224, 1040	1688	1372	728.86/ 730.83/ 732.85
3e	NO_2,H	20	251-253	15	3632, 3102	1626	1751	1212, 1049	1710	1347	593.90**
3f	Cl,NO_2	31	256-258	15	3365, 3101	1633	1742	1243, 1041	1710	1375	652.00/ 653.96
3g	Br,NO_2	35	260-261	8	3358, 3093	1627	1744	1229, 1040	1720	1373	695.91/ 697.94

*$[M+H]^+$, **$[M-H]^+$.

IR spectra 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 ^1H and ^{13}C were confirmed using HMBC and HSQC methods (for compound **3d**). The ^1H 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 2). The ^{13}C NMR spectrum of compound **3d**, 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 3). Peak of molecular ion of these thiosemicarbazones showed the mass number which is coincided to its molecular weight (table 1).

In summary, we reported for the first time a microwave-assisted and efficient method for synthesis of (2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiosemicarbazones of substituted isatins.

Table 2: ^{1}H-NMR spectral data of compounds **3a–g**

Proton	R^1=R^2=H **(3a)**	R^1=5-Cl, R^2=H **(3b)**	R^1=Br, R^2=H **(3c)**	R^1=R^2=5,7-Br **(3d)**	R^1=NO_2, R^2=H **(3e)**	R^1=5-Cl, R^2=NO_2 **(3f)**	R^1=5-Br, R^2=NO_2 **(3g)**
NH_b	12.77,s	12.61,s	12.64,s	12.56,s	12.59,s	12.44,s	12.45,s
NH isatin	11.21,d	11.32,s	11.33,s	11.67,s	11.83,s	11.99,s	11.99,s
NH_a	9.52,d,9.0	9.67,d,9.5	9.77,d,9.0	9.75,d,9.0	9.90,d,9.0	9.85,d,9.0	9.86,d,9.5
H-4’	7.72,d,7.5	7.82,s	7.99,d,1.5	7.96,s	8.63,d,2.5	8.16,d,2.25	8.27,s
H-5’	6.94,d,8.0	-		-	-	-	-
H-6’	7.12,dt,7.5,0.5	7.42,dd,8.5,1.5	7.54,dd,8.0,2.0	7.82,s	8.30,dd,8.5,2.5	8.23,d,2.25	8.34,d,1.5
H-7’	7.39,dt,7.5,1.0	6.95,d,8.0	6.91,d,8.0	-	7.13,d,9.0	-	-
H-1	5.99,t,9.0	6.03,t,9.0	5.98,t,9.0	6.03,t,9.25	6.06,t,9.25	6.05,t,9.25	6.05,t,9.25
H-3	5.44,t,9.5	5.46,t,9.0	5.42-5.35,m	5.46,t,9.25	5.47,t,9.5	5.48,t,9.5	5.48,t,9.5
H-2	5.33,t,9.25	5.32,t,9.25		5.32,t,9.25	5.35,t,9.25	5.31,t,9.25	5.32,t,9.25
H-4	4.98,t,9.75	4.99,t,9.5		4.99,t,9.75	5.01,t,9.75	5.00,t,9.75	5.00,t,9.5
H-5	4.14,dq,9.5,2.5	4.19,d,10.0	4.35,m	4.19,d,9.5	4.19,dq,10.0,2.0	4.20,dq,10.0,2.0	4.20,dq,10.0,2.0
H-6a	4.23,dd,12.5,4.5	4.24,dd,12.5,4.5	4.40,t,6.5	4.24,dd,12.5,4.5	4.24,dd,12.5,5.0	4.25,dd,12.25,4.75	4.25,dd,12.25,4.75
H-6b	4.01,dd,12.5,1.65	4.01,d,11.5	4.08,d,6.5	4.01,d,11.5	4.01,dd,12.25,1.75	4.02,d,11.0	4.01,dd,11.0,1.5
4×CH_3CO	2.01–1.93	2.01–1.93	2.16–1.95	2.01–1.93	2.02–1.93	2.01–1.93	2.02–1.93

Table 3: ^{13}C-NMR spectral data of compounds **3a–g**

Carbon	R^1=R^2=H (**3a**)	R^1=5-Cl, R^2=H (**3b**)	R^1=Br, R^2=H (**3c**)	R^1=R^2=5,7-Br (**3d**)	R^1=NO_2, R^2=H (**3e**)	R^1=5-Cl, R^2=NO_2 (**3f**)	R^1=5-Br, R^2=NO_2 (**3g**)
C=S	179.01	179.00	179.09	178.99	178.01	178.96	178.95
4x*CO*CH$_3$	169.84–169.21	169.99–169.23	169.98–169.35	169.98–169.19	169.93–169.14	169.90–169.11	169.90–169.11
C=O amit	162.44	162.33	162.19	162.33	162.88	162.60	162.49
C-3'	133.25	132.13	133.66	135.10	131.45	136.60	136.95
C-4'	121.24	121.63	123.82	131.67	116.69	129.41	129.32
C-4a'	119.61	112.69	122.05	114.45	120.71	125.38	125.60
C-5'	111.09	126.60	114.18	104.28	142.76	113.13	113.13
C-6'	122.30	130.95	131.90	122.71	127.34	126.07	127.02
C-7'	131.66	120.93	113.07	123.51	111.30	132.01	132.32
C-7a'	142.65	141.37	141.69	141.08	147.73	126.07	128.72
C-1	81.79	81.86	82.36	81.88	81.97	81.87	81.89
C-2	70.88	71.00	68.64	70.99	70.94	70.97	70.96
C-3	72.68	72.72	71.97	72.72	72.72	72.64	72.65
C-4	67.77	67.68	67.48	67.65	67.64	67.61	67.61
C-5	72.40	72.48	70.72	72.50	72.53	72.50	72.50
C-6	61.13	61.67	61.32	61.66	61.65	61.60	61.60
4×*CH$_3$*CO	20.40-20.18	20.53-20.31	20.49-18.49	20.53-20.32	20.49-20.28	20.71-20.25	20.48-20.25

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