J. Serb. Chem. Soc. 71 (6) 581–585 (2006) UDC 547.789.1:54.066
JSCS–3451 *Note*

NOTE

Synthesis of new 3-(2-aminothiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one derivatives

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(Received 20 June, revised 12 October 2005)

Abstract: Aminothiazole derivatives of 4-hydroxy-2*H*-chromen-2-one were prepared by the Hantzsch reaction[1] using 3-(2-bromoacetyl)-4-hydroxy-2*H*-chromen-2-one and thiourea derivatives. Starting compound for this synthesis 3-(2-bromoacetyl)-4-hydroxy-2*H*-chromen-2-one (**1**) was prepared previously.[2] Also, for this synthesis we used thiourea derivatives (**2a**–**j**) as compounds which possess groups with biological activity. Reactions are carried out in refluxing ethanol for a period of 30 – 45 min. Final products (**3a**–**j**) are obtained in a high yield. Chemical structure of the obtained compounds was confirmed by elemental and structural analysis (IR and ^{1}H NMR spectroscopy).

Keywords: Hantzsch reaction, 3-(2-aminothiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one derivatives.

INTRODUCTION

2-Aminothiazoles are among the most important compounds in pharmacology. Some of these compounds possess anthelmintic activity, such as thiabedazole.[3] Sulphathiazole[3] possesses antibiotic activity. Nizatidine,[3] a compound which possesses the thiazole moiety, has clinical use as an antiulcer drug. Farnetiaole[3] has significant immunosupressant activity, while fentiasac[3] has clinical use as an anti-inflammatory agent. Recent research indicates that some of 2-aminothiazoline derivatives are inhibitors of enzymes such as kinurenine-3-hydroxylase[4] or possess inhibitory activity against the enzyme cyclin-dependent kinase.[5]

On the other hand, several coumarin derivatives have pronounced medicinal value as antibacterial and antifungal agents.[6,7] Others display antitubercular activity[8] or show insecticidal properties.[9] The compounds have very important pharmaceutical value because of their anticoagulant and antitumor activities.[10–12]

The approach to the preparation of potential biologically active compounds today is predominantly based on the combination of different substructures which

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doi: 10.2298/JSC0606581S

increased the biological activity of known active substances. The reason for one such synthesis in this study is based on the fact that 4-hydroxycoumarine derivatives possess anticoagulant activity while aminothiazole derivatives of 4-hydroxycoumarines possess significant antibacterial activity (investigation of the antibacterial activity of the synthesized compounds are currently in progress).

The starting compound 3-(2-bromoacetyl)-4-hydroxy-2*H*-chromen-2-one (**1**) reacts with thiourea derivatives (**2a–j**) in equimolar amounts in refluxing ethanol as the reaction medium to give the corresponding aminothiazole derivatives of 4-hydroxy-2*H*-chromen-2-one (**3a–j**) in a good yield (Scheme 1). The structure of the synthesized compounds was determined on the basis of spectral data and elemental analysis (Tables I–IV). Characteristic absorptions for the OH, NH, C = O and C = N groups were observed in the IR spectra. In the ^{1}H NMR spectrum, one isolated singlet was observed (for thiazoline H-5'). This singlet is evidence for the existence of the thiazole moiety.

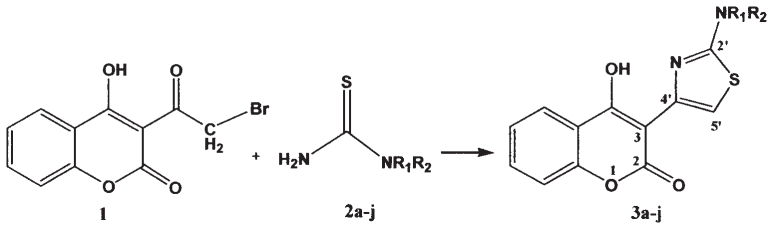
The obtained results indicate that the Hantzsch reaction in this case represents an easy and efficient method for forming the heterocyclic moiety on the 3-position of the coumarin ring.

TABLE I. Nature of R_1 and R_2 in thiourea derivatives **2a–j** and the reaction products **3a–j**

R_1	R_2	Names of products	**3a–j**
H	$C_6H_3(OH)COOH$	2-Hydroxy-4-[4-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-thiazol-2-ylamino]benzoic acid	**3a**
H	*p*-$C_6H_4NO_2$	4-Hydroxy-3-[2-(4-nitrophenylamino)-thiazol-4-yl]-2*H*-chromen-2-one	**3b**
H	*p*-$C_6H_4SO_3H$	4-[4-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)thiazol-2-ylamino]benzenesulfonic acid	**3c**
H	*m*-$C_6H_4CH_3$	4-Hydroxy-3-(2-*m*-tolylaminothiazol-4-yl)-2*H*-chromen-2-one	**3d**
H	$(CH_2)_4COOH$	5-[4-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)thiazol-2-ylamino]pentanoic acid	**3e**
Et	Et	3-(2-Diethylamino-thiazol-4-yl)-4-hydroxy-2*H*-chromen-2-one	**3f**
acetyl	C_6H_5	*N*-[4-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)thiazol-2-yl]-*N*-phenylacetamide	**3g**
H	*m*-$C_6H_4CH_3$	4-Hydroxy-3-(2-*o*-tolylaminothiazol-4-yl)-2*H*-chromen-2-one	**3h**
H	*m*-$C_6H_4NO_2$	4-Hydroxy-3-[2-(3-nitrophenylamino)thiazol-4-yl]-2*H*-chromen-2-one	**3i**
H	$C_{10}H_7$	4-Hydroxy-3-(2-(naphth-1-ylamino)thiazol-4-yl)-2*H*-chromen-2-one	**3j**

EXPERIMENTAL

Melting points (m.p.) were recorded on a Kofler–hot stage apparatus and are uncorrected. Microanalysis for carbon, hydrogen and nitrogen was carried out with a Carlo Erba 1106 microanalyser. The IR spectra were run on a Perkin-Elmer grating spectrophotometers Model 137 and Model 337, ν in cm^{-1}. The NMR spectra were recorded on a Varian Gemini 200 spectrometer (^{1}H at



Scheme 1. Reagents and conditions: thiourea derivatives (**2a-j**), ethanol, reflux, 30–45 min.

200 MHz) in DMSO-d_6 using TMS ($SiMe_4$) as the internal standard. Chemical shifts (δ) are given in ppm, abbreviations: *s*-singlet, *d*-doublet, *t*-triplet, *q*-quartet, *m*-multiplet. Abbreviations used: DMSO-dimethyl sulphoxide, EtOH-ethanol. The reactions were monitored by thin-layer chromatography (TLC) using silica gel G after Stahl.

*Preparation of 2-aminothiazole derivatives of 4-hydroxy-2*H*-chromen-2-one* (**3a–j**)

To a solution of 3-(2-bromoacetyl)-4-hydroxy-2*H*-chromen-2-one (**1**) (1 g, 3.5 mmol) in absolute ethanol (60 ml), the required thiourea derivative (**2a–j**) was added (3.5 mmol). The mixture was refluxed for 30 – 45 min. After cooling, the precipitate was collected and the final crystalline product was recrystallized from 96 % EtOH.

TABLE II. Characterization of the prepared compounds

Compound	Formula	Mol.wt.	w_i(calc.)/%, w_i (found)/%			Yield	M.p.*
			C	H	N	% (g)	°C
3a	$C_{19}H_{12}N_2O_6S$	396.37	57.57	3.05	7.07	79.00 (1.10)	280–285
			56.90	3.01	7.14		
3b	$C_{18}H_{11}N_3O_5S$	381.36	56.69	2.91	11.02	82.70 (1.10)	225–232
			57.05	2.93	10.95		
3c	$C_{18}H_{12}N_2O_6S_2$	416.43	51.92	2.90	6.73	72.40 (1.05)	245–250
			51.90	2.87	6.75		
3d	$C_{19}H_{14}N_2O_3S$	350.39	65.13	4.02	7.99	84.00 (1.03)	270–275
			65.10	3.99	8.03		
3e	$C_{17}H_{16}N_2O_5S$	360.38	56.66	4.47	7.77	71.43 (0.90)	220–225
			57.01	4.23	7.58		
3f	$C_{16}H_{16}N_2O_3S$	316.37	60.74	5.10	8.85	63.04 (0.70)	245–247
			60.70	5.15	8.82		
3g	$C_{20}H_{14}N_2O_4S$	378.40	63.48	3.73	7.40	46.97 (0.62)	215–220
			63.50	3.72	7.45		
3h	$C_{19}H_{14}N_2O_3S$	350.39	65.13	4.03	7.99	54.63 (0.67)	236–240
			65.09	3.97	8.05		
3i	$C_{18}H_{11}N_3O_5S$	381.36	56.69	2.91	11.02	67.47 (0.90)	> 300
			57.07	2.85	10.98		
3j	$C_{22}H_{14}N_2O_3S$	386.42	68.38	3.65	7.25	82.81 (1.12)	276–280
			68.29	3.72	7.29		

*Estimated values for m.p. are uncorrected

TABLE III. Specific IR spectral data* of the synthesized compounds

Comp.	ν_{max}/cm^{-1}
3a	3413 (NH; OH), 3187 (OH), 3028 (=CH_2), 1676 (C=O), 1605 (C=N)
3b	3414 (OH; NH), 3072 (=CH), 1726 (C=O), 1600 (C=N), 1608 and 1369 (NO_2)
3c	3436 (NH; OH), 3180 (OH), 1694 (C=O), 1600 (C=N), 1099 (S=O)
3d	3412 (NH; OH), 3067 (=CH), 2974 and 2938 (CH_3), 1681 (C=O), 1607 (C=N)
3e	3416 (NH; OH), 3114 (OH), 3084 (=CH), 2926 and 2853 (CH_2), 1690 (C=O), 1614 (C=N)
3f	3413 (NH; OH), 3067 (=CH), 2954 (CH_3,CH_2), 1681 (C=O), 1603 (C=N)
3g	3414 (NH; OH), 3082 (=CH), 2974 and 2938 (CH_3), 1650 and 1613 (C=O), 1601 (C=N)
3h	3414 (NH), 3301 (OH), 3040 (=CH), 2982 (CH_3), 1690 (C=O), 1605 (C=N)
3i	3415 (NH), 3279 (OH), 3083 (=CH), 1675 (C=O), 1615 and 1352 (NO_2)
3j	3413 (NH), 3287 (OH), 3054 (=CH), 1693 (C=O), 1607 (C=N)

*IR spectra were recorded in KBr discs

TABLE IV. Specific ^{1}H NMR spectral data* of the synthesized compounds

Comp.	δ(ppm)
3a	7.83 (*s*, 1H, C-5'-H), 13.27 (*s*, 1H, C-4-OH), 12.11 (*s*, 1H, C-2'-NH), 13.41 (*s*, 1H, C-6"-OH), 8.1 (*s*, 1H, C-4"-OH), 7.30–7.83 (*m*, 4H, C-5-H, C-6-H, C-7-H, C-8-H)
3b	8.10 (*s*, 1H, C-5'-H), 13.25 (*s*, 1H, C-4-OH), 10.22 (*s*, 1H, C-2'-NH), 7.30–7.83 (*m*, 4H, C-5-H, C-6-H, C-7-H, C-8-H)
3c	7.78 (*s*, 1H, C-5'-H), 13.24 (*s*, 1H, C-4-OH), 10.94 (*s*, 1H, C-2-NH), 10.31 (*s*, 1H, OH), 7.30–7.83 (*m*, 4H, C-5-H, C-6-H, C-7-H, C-8-H)
3d	8.08 (*s*, 1H, C-5'-H), 15.30 (*s*, 1H, C-4-OH), 9.60 (*s*, 1H, C-2'-NH), 6.60–7.82 (*m*, 4H, C-5-H, C-6-H, C-7-H, C-8-H and phenyl), 2.20 (*s*, 3H, CH_3)
3e	7.90 (*s*, 1H, C-5'-H), 14.98 (*s*, 1H, C-4-OH), 5.87 (*s*, 1H, C-2'-NH), 9.26 (*s*, 1H, C-5"OH), 7.30–7.83 (*m*, 4H, C-5-H, C-6-H, C-7-H, C-8-H)
3f	7.64 (*s*, 1H, C-5'-H), 14.89 (*s*, 1H, C-4-OH), 3.11 (*q*, 2H, C-1"-H), 1.04 (*t*, 3H, C-2"-H), 7.30–7.83 (*m*, 4H, C-5-H, C-6-H, C-7-H, C-8-H)
3g	7.40 (*s*, 1H, C-5'-H), 14.89 (*s*, 1H, C-4-OH), 2.60 (*s*, 3H, CH_3), 7.05–7.83 (*m*, 4H, C-5-H, C-6-H, C-7-H, C-8-H and phenyl)
3h	7.85 (*s*, 1H, C-5'-H), 14.80 (*s*, 1H, C-4-OH), 9.20 (*s*, 1H, C-2'-NH), 6.67–7.82 (*m*, 4H, C-5-H, C-6-H, C-7-H, C-8-H and phenyl), 2.10 (*s*, 3H, CH_3)
3i	7.91 (*s*, 1H, C-5'-H), 14.15 (*s*, 1H, C-4-OH), 8.74 (*s*, 1H, C-2'-NH), 7.16–7.76 (*m*, 4H, C-5-H, C-6-H, C-7-H, C-8-H)
3j	7.87 (*s*, 1H, C-5'-H), 15.54 (*s*, 1H, C-4-OH) 8.57 (*s*, 1H, C-2'-NH), 7.14–8.01 (*m*, 4H, C-5-H, C-6-H, C-7-H, C-8-H)

*^{1} H NMR spectra were recorded using DMSO-d_6 as the solvent and TMS as the internal standard

ИЗВОД

СИНТЕЗА НОВИХ ДЕРИВАТА 3-(2-АМИНОТИАЗОЛ-4-ИЛ)-4-ХИДРОКСИ-2*H*-ХРОМЕН-2-ОНА

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У овом раду представљена је изузетно ефикасна метода синтезе нових 2-аминотиазолских деривата 4-хидроксикумарина. Експериментална мерења су потврдила висок принос и једнозначност реакције у случају свих синтетисаних кумаринских деривата.

(Примљено 20. јуна, ревидирано 12. октобра 2005)

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