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CHEMISTRY OF HETERO ANALOGS OF ISOFLAVONES 26*. SYNTHESIS OF 2-ALKYL DERIVATIVES OF 3-(THIAZOL-2-YL)- AND 3-(BENZOTHIAZOL-2-YL)CHROMONES

M. S. Frasinyuk[1] and V. P. Khilya[2]

Treatment of substituted 2-(2,4-dihydroxyphenacyl)thiazole and 2-(2,4-dihydroxyphenacyl)benzothiazole with propionic and isobutyric anhydrides gives the substituted 2-ethyl- and 2-isopropyl-7-acyloxychromones. The use of pivaloyl chloride gives 1-pivaloyloxy-2-hetarylstyrene derivatives.

Keywords: 2-alkylchromones, acid anhydrides (chlorides), O-acylenols, hetero analogs of isoflavones.

Amongst frequently occurring natural compounds of plant origins an important place is occupied by the class of flavonoids, one or another representatives of which occurs in virtually all kinds of plants [2]. Greater attention has been focussed in recent times on the methods of synthesis and modification of both natural isoflavonoids and their synthetic analogs and hetero analogs.

For the overwhelming majority of examples of synthesis of 2-alkylchromones the reaction of 2-hydroxydeoxybenzoins with acylating agents has been used, most frequently with acetic and trifluoroacetic anhydride. Individual cases are known where derivatives of propionic acid and its homologs have been employed in the synthesis of 2-alkylchromones [3-6]. Other synthetic routes are used extremely rarely, e.g. in the rearrangement of α-methyl substituted chalcones to 2-methylisoflavones with $Tl(NO_3)_3$ [7, 8].

In the last decade an increased interest has occurred in the synthesis of 2-(ω-carboxyalkyl)isoflavones which have found application in immunology thanks to the presence of the carboxyl group in the 2-alkyl chain which can associate with proteins and change their stereochemical and electronic parameters [9-11].

We have found that reaction of 2-(2,4-dihydroxyphenacyl)-1-methylbenzimidazole with aliphatic acid anhydrides (chlorides) gives exclusively 2-alkyl-3-(1-methylbenzimidazol-2-yl)chromones [1].

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* For Communication 25 see [1].

[1]Institute of Bioorganic and Petroleum Chemistry, National Academy of Sciences of Ukraine, Kiev 02094; e-mail: mfras@i.kiev.ua. [2]Taras Shevchenko National University, Kiev 01033, Ukraine; e-mail: vkhilya@mail.univ.kiev.ua. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 6, pp. 835-840, June, 2008. Original article submitted December 16, 2007.

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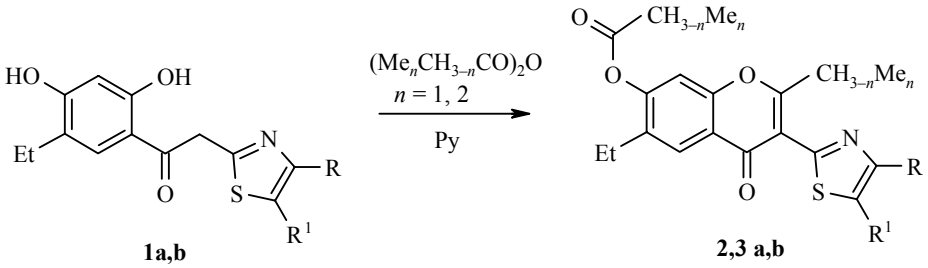
Bearing in mind the fact that the structure of the reaction products of deoxybenzoins with carboxylic acid derivatives depends to a marked extent on the activity of the methylene group in the starting deoxybenzoin (number of free hydroxyl groups and substituents [12]) and on the acylation reagent used we have now studied the interaction of the 2-(2,4-dihydroxy-5-ethylphenacyl)-4-methylthiazole (**1a**) [13] and 2-(2,4-dihydroxy-5-ethylphenacyl)benzothiazole (**1b**) [14] with aliphatic acid anhydrides and chlorides.

Prolonged holding of compounds **1a,b** with a marked excess of propionic or isobutyric anhydride in pyridine gives the corresponding 7-acyloxy derivatives of 2-ethyl- or 2-isopropyl-3-hetarylchromones **2a,b** or **3a,b** respectively. The ^{1}H NMR spectra of compounds **2, 3** show the absence of signals for the methylene and hydroxyl groups and the appearance of signals for the protons of two residues of the acid used. The signals for the methyl protons in the 2-isopropyl group in compounds **3a,b** are seen as a doublet pointing to their equivalence and to the absence of a chiral axis due to hindered rotation as was observed in the case of isoflavones having bulky substituents in positions 2 and 3 [15, 16].

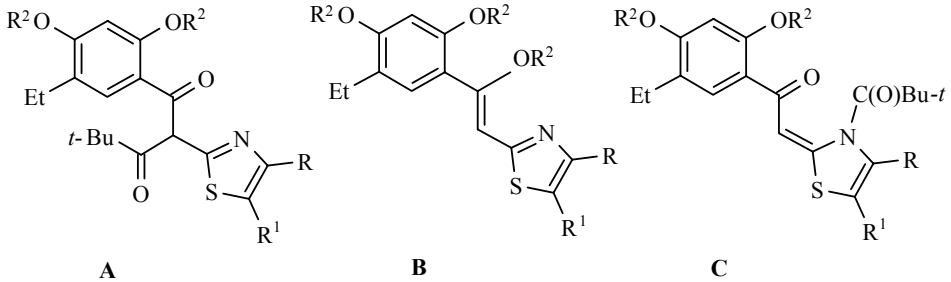
The use of pivaloyl chloride, both at room temperature and upon heating, did not give 2-*tert*-butyl-3-hetarylchromones as was the case for the synthesis of 2-*tert*-butyl-3-(benzimidazol-2-yl)chromones [1]. The ^{1}H NMR spectra of the compounds formed showed a one proton singlet at 6.78 and 6.90 ppm as well as signals for three pivalic acid residues. With the preceding investigation of the acetylation of 2-hydroxydeoxybenzoins [17, 18] and the structures of the starting compounds **1a,b** in mind we can propose that the acylation involves the phenol hydroxyls and also the methylene unit (type **A**) or enol hydroxyl (type **B**). We do not exclude that the presence of the (benzo)thiazole ring can make possible an acylation to form an N-acyl-2-methylene-2,3-dihydro(benzo)thiazole of type **C**.



1a,b **2,3 a,b**

1-3 a R = Me, R^1 = H; **b** RR^1 = CH=CH–CH=CH; **2a,b** *n* = 1, **3a,b** *n* = 2

A choice of route for the reaction could be made between **A**-**C** in this case on the basis of the ^{13}C NMR spectroscopic data for the synthesized compounds as well as for compounds **2, 3** (Table 1). It was found that here the acylation occurs to give the acyl derivatives at the enol hydroxyl **4a,b** as type **B**.



A **B** **C**

4 a R = Me, R^1 = H; **b** RR^1 = CH=CH–CH=CH; **4a,b** R^2 = *t*-BuCO

TABLE 1. ^{13}C NMR Spectroscopic Characteristics for Compounds **2a,b-4a,b**

Compound	Chemical shifts, δ ppm, in $CDCl_3$																	
	Phenol fragment										(Benzo)thiazole fragment							see Footnotes
	C-2	C-3	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a	Et-6	C-2	C-4a	C-4	C-5	C-6	C-7	C-7a	
2a	171.8	115.4	175.1	120.5	126.2	134.2	153.0	111.1	153.9	13.8, 22.9	157.5		151.2	115.4				172.1*, 27.7*2, 27.2*2, 11.5*3, 9.1*3, 17.2*4
2b	172.1	115.5	175.3	120.6	126.4	134.6	153.3	111.3	154.1	13.9, 23.0	159.7	151.9	123.0	124.9	125.70	121.3	136.1	173.5*, 27.8*2, 27.6*2, 11.7*3, 9.1*3
3a	174.2	114.8	174.8	120.6	126.3	134.3	153.1	111.1	154.1	14.0, 23.0	157.6		151.5	115.6				175.4*, 34.3*2, 31.1*2, 20.0*3, 18.9*3, 17.3*4
3b	175.4	114.8	174.6	120.5	126.3	134.6	153.3	111.1	154.1	13.9, 22.9	159.7	151.9	123.0	124.9	125.6	121.2	136.2	175.4*, 34.4*2, 31.2*2, 20.0*3, 18.8*3
4a	–	117.4 (C-2)	145.8 (C-1)	126.3 (C-1')	129.6 (C-6')	133.3 (C-5')	149.5 (C-4')	114.3 (C-3')	146.6 (C-2')	15.0, 22.8	160.0		152.9	116.1				176.4*, 175.3*, 39.2*2, 27.2*3, 17.0*4
4b	–	117.5 (C-2)	146.8 (C-1)	126.2 (C-1')	129.6 (C-6')	133.5 (C-5')	149.9 (C-4')	116.5 (C-3')	148.5 (C-2')	14.0, 22.9	160.7	152.9	123.3	125.4	126.3	121.4	135.2	176.3*, 176.2*, 39.3*2, 27.2*3

* COO.

*2 C(2)–C–C and C–COO-7.

*3 C(2)–C–C and C–C–COO-7.

*4 CH_3-4 thiazole.

Attempts to convert compounds **4a,b** to 2-*tert*-butylchromone derivatives using base [17] were unsuccessful, the reaction products proving to be the starting desoxybenzoins **1a,b**.

Hence we have studied the reaction of 2-(5-ethyl-2,4-dihydroxyphenacyl)thiazole and an annelated analog with aliphatic acid anhydrides (chlorides). The use of propionic or isobutyric acid anhydrides makes possible the synthesis of substituted 2-ethyl- and 2-isopropyl-3-hetarylchromones. Introduction of the bulkier pivaloyl chloride into the reaction leads to formation of 1-pivaloyloxy-2-((benzo)thiazol-2-yl)styrene.

EXPERIMENTAL

Monitoring of the reaction course and evaluation of the purity of the compounds obtained was carried out by TLC on Silufol UV-254 and Merck plates. The eluents used were a mixture of chloroform and methanol (9:1 and 95:5) or of hexane and ethyl acetate (1:2). ^{1}H NMR and ^{13}C NMR spectra were taken on a Varian VXR 300 instrument (300 and 75 MHz respectively) using $CDCl_3$ and with TMS as internal standard.

Synthesis of compounds 2-4 a,b (General Method). A mixture of the starting ketone **1a,b** (10 mmol) the corresponding acid anhydride or chloride (50-60 mmol) and absolute pyridine (25 ml) was held for 48-72 h at room temperature (the end of the reaction being judged by TLC). The reaction mixture was poured onto ice and the precipitate after solidification was filtered off, dried, and crystallized from hexane.

3-(4-Methyl-1,3-thiazol-2-yl)-4-oxo-2,6-diethyl-4H-chromen-7-yl Propionate (2a). Yield 49%; mp 107-108ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.26, 1.32, 1.37 (9H, three t, *J* = 7.2, 1-$CH_2C\underline{H}_3$, 6-$CH_2C\underline{H}_3$, and $C\underline{H}_3CH_2CO$); 2.51 (3H, s, 4'-CH_3); 2.63, 2.69 (4H, two q, *J* = 7.2, $MeC\underline{H}_2CO$ and 6-$C\underline{H}_2Me$); 3.36 (2H, q, *J* = 7.2, 2-$C\underline{H}_2Me$); 7.02 (1H, s, H-5'); 7.28 (1H, s, H-8); 8.15 (1H, s, H-5). Found, %: N 3.77; S 8.63. $C_{20}H_{21}NO_4S$. Calculated, %: N 3.52; S 8.68.

3-(1,3-Benzothiazol-2-yl)-4-oxo-2,6-diethyl-4H-chromen-7-yl Propionate (2b). Yield 54%; mp 151-153ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.28, 1.33, 1.43 (9H, three t, *J* = 7.2, 2-$CH_2C\underline{H}_3$, 6-$CH_2C\underline{H}_3$, and $C\underline{H}_3CH_2CO$); 2.68 (4H, m, $MeC\underline{H}_2CO$ and 6-$C\underline{H}_2Me$); 3.44 (2H, q, *J* = 7.2, 2-$C\underline{H}_2Me$); 7.31 (1H, s, H-8); 7.40, 7.49 (2H, two m, H-4', H-7'); 7.98, 8.07 (2H, two m, H-5',6'); 8.21 (1H, s, H-5). Found, %: N 3.44; S 7.87. $C_{23}H_{21}NO_4S$. Calculated, %: N 3.45; S 7.73.

2-Isopropyl-3-(4-methyl-1,3-thiazol-2-yl)-4-oxo-6-ethyl-4H-chromen-7-yl 2-Methylpropionate (3a). Yield 58%; mp 165-167ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.26 (3H, t, *J* = 7.2, 6-$CH_2C\underline{H}_3$); 1.35, 1.38 (12H, two d, *J* = 7.2, 2-$CH(C\underline{H}_3)_2$ and $(CH_3)_2CHO$); 2.51 (3H, s, 4'-Me); 2.65 (2H, q, *J* = 7.2, 6-$C\underline{H}_2Me$); 2.90 (1H, m, $Me_2C\underline{H}CO$); 4.26 (1H, m, 2-$C\underline{H}Me_2$); 7.04 (1H, s, H-5'); 7.28 (1H, s, H-8); 8.16 (1H, s, H-5). Found, %: N 3.51; S 8.03. $C_{22}H_{25}NO_4S$. Calculated, %: N 3.40; S 8.23.

3-(1,3-Benzothiazol-2-yl)-2-isopropyl-4-oxo-6-ethyl-4H-chromen-7-yl 2-Methylpropionate (3b). Yield 47%; mp 174-176ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.29 (3H, t, *J* = 7.2, 6-$CH_2C\underline{H}_3$); 1.39 (12H, d, *J* = 7.2, 2-$CH(C\underline{H}_3)_2$ and $(C\underline{H}_3)_2CHCO$); 2.67 (2H, q, *J* = 7.2, 6-$C\underline{H}_2Me$); 2.91 (1H, d, $Me_2C\underline{H}CO$); 4.27 (1H, m, 2-$CHMe_2$); 7.32 (1H, s, H-8); 7.41, 7.50 (2H, two m, H-4', 7'); 7.97, 8.08 (2H, two m, H-5', 6'); 8.18 (1H, s, H-5). Found, %: N 3.22; S 7.36. $C_{25}H_{25}NO_4S$. Calculated, %: N 3.05; S 7.39.

1-{2,4-Bis[(2,2-dimethylpropanoyl)oxy]-5-ethylphenyl}-2-(4-methyl-1,3-thiazol-2-yl)ethenyl Pivalate (4a). Yield 65%; mp 96-97ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.18 (3H, t, *J* = 7.2, 5'-$CH_2C\underline{H}_3$); 1.32 (9H, s, 1-$CCOO(CH_3)_3$); 1.38 (18H, s, 2'-$CCOO(CH_3)_3$ and 4'-$CCOO(CH_3)_3$); 2.45 (3H, s, 4''-CH_3); 2.55 (2H, q, *J* = 7.2, 5'-$C\underline{H}_2Me$); 6.78 (1H, s, H-2); 6.86 (1H, s, H-3'), 6.88 (1H, s, H-5''); 7.35 (1H, s, H-6'). Found, %: N 2.64; S 6.05. $C_{29}H_{39}NO_6S$. Calculated, %: N 2.50; S 6.15.

2-(1,3-Benzothiazol-2-yl)-1-{2,4-bis[2,2-dimethylpropanoyl]oxy}-5-ethylphenyl}ethenyl Pivalate (4b). Yield 72%; mp 163-164ºC. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.20 (3H, t, *J* = 7.2, 5'-$CH_2C\underline{H}_3$); 1.33 (9H, s,

1-CCOO(CH_3)$_3$) 1.38, 1.42 (18H, two s, 2'-CCOO(CH_3)$_3$ and 4'-CCOO(CH_3)$_3$); 2.54 (2H, q, J = 7.2, 5'-C$\underline{H_2}$Me); 6.90 (1H, s, H-2); 6.92 (1H, s, H-3'); 7.38 (1H, s, H-6'); 7.40, 7.49 (2H, two m, H-4", 7"); 8.01, 8.03 (2H, two m, H-5", 6"). Found, %: N 2.48; S 5.67. $C_{32}H_{39}NO_6S$. Calculated, %: N 2.63; S 5.50.

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