Chemistry of Heterocyclic Compounds, Vol. 45, No. 3, 2009

SYNTHESIS AND PROPERTIES OF 4-CHLOROMETHYL-6-HYDROXY-COUMARINS AND 4-(2-BENZOFURYL)-6-HYDROXYCOUMARINS

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New 4-chloromethyl-6-hydroxycoumarins have been obtained by the condensation of hydroquinone derivatives with 4-chloroacetoacetic ester, and have been used for the synthesis of 4-(2-benzofuryl)-6-hydroxycoumarins. Alkylation and acylation of the phenolic hydroxyl of the synthesized 4-(2-benzofuryl)coumarins have been investigated.

Keywords: 4-(2-benzofuryl)coumarins, 4-chloromethylcoumarins, alkylation, acylation, heterocyclization.

4-Halomethylcoumarins, which may be obtained under the conditions of the Pechmann reaction [1-3] by the chlorination of derivatives of coumarin-4-acetic acid in AcOH [4] and by the interaction of 4-hydroxymethylcoumarins with PCl_5 in benzene [5], are convenient reactants for the synthesis of various heterocyclic compounds. Substituted chloromethylcoumarins are converted into derivatives of 3-benzofurylacetic acid by the action of alkalis [6]. The alkylation of amines and phenols by substituted 4-halomethylcoumarins is known [7-11].

Various methods have been described for the synthesis of 4-(2-benzofuryl)coumarins including alkylation with 4-halomethylcoumarins of salicylaldehyde derivatives [12-15], of 2-hydroxyacetophenone [16], or methyl salicylate [16] with subsequent intramolecular cyclization of the methylene and carbonyl groups, interaction of 2-(2-hydroxybenzoyl)benzofuran with ethyl (triphenylphosphorylidene)acetate [13], or Pechmann condensation of resorcinol with 2-benzofuroylacetic ester [13]. At the present moment only the last method permits derivatives of 2-benzofurylcoumarin containing a free hydroxyl group to be obtained.

In this connection it was of interest to study the possibility of using 4-(2-benzofuryl)hydroxycoumarins without previous protection of the phenolic hydroxyl group for the synthesis of 4-chloromethylcoumarins. To achieve this aim we synthesized the new 4-chloromethyl-6-hydroxycoumarins **1a-c**, and also used the previously described 4-chloromethyl-7-hydroxycoumarins **1d,e** [6].

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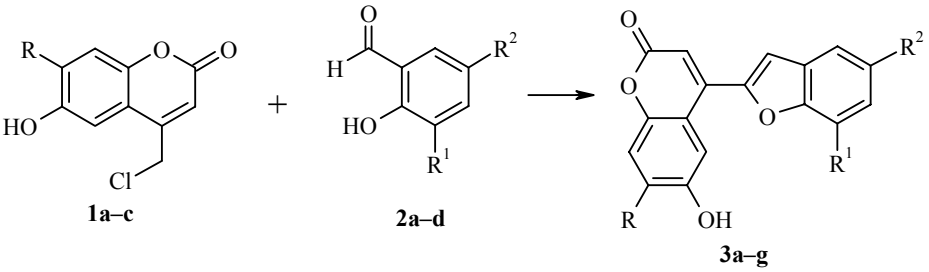
Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 361-369, March, 2009. Original article submitted November 27, 2007.

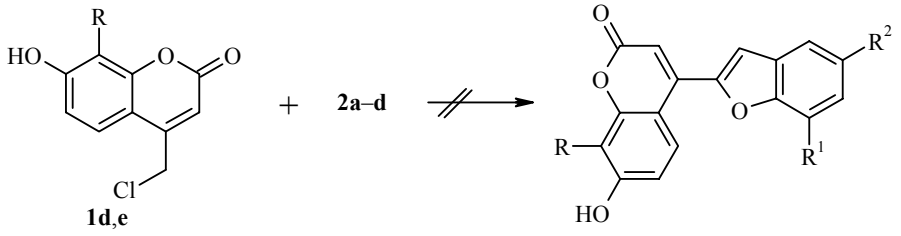
 0009-3122/09/4503-0290

As it turned out, the interaction of substituted 4-chloromethyl-6-hydroxycoumarins **1a-c** with salicylaldehydes **2a-d** was effected in DMF in the presence of potassium carbonate. This alkylation reaction proceeds selectively with the formation of 4-(2-benzofuryl)-6-hydroxycoumarins **3a-g**. Alkylation of the hydroxyl group of substituted 4-chloromethyl-6-hydroxycoumarins was not observed. To all appearances this is caused by the lower reactivity of the phenolic hydroxyl in position 6 of the coumarin compared with the hydroxyl group of salicylaldehyde.



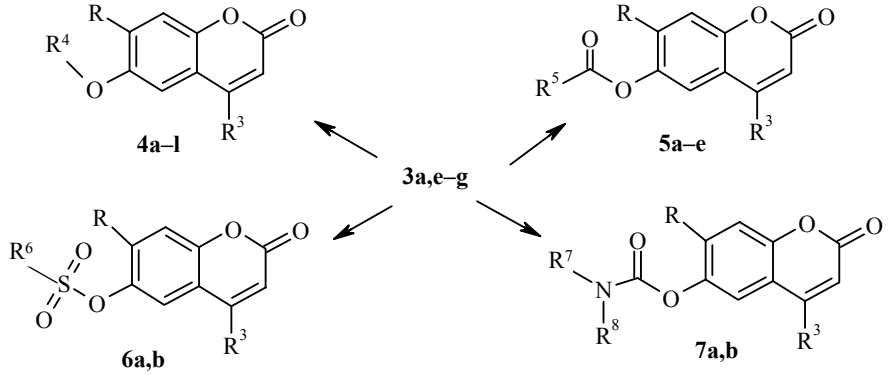
1a, **3a**,**c**,**g** R = H, **1b**, **3b**,**d**,**f** R = Me, **1c**, **3e** R = Ph; **2a**, **3a**,**b** $R^1 = R^2 = H$;
2b, **3c–e** R^1 = OMe, R^2 = H; **2c**, **3f** R^1 = OEt, R^2 = H; **2d**, **3g** R^1 = H, R^2 = Br

At the same time the interaction of 4-chloromethyl-7-hydroxycoumarins [6] with salicylaldehydes under analogous conditions led to the formation of a mixture of difficultly separable products.



1 **d** R = H, **e** R = Me

In view of the special features of the structure of the synthesized compounds **3a-e,g**, we studied their reaction at the phenolic hydroxyl. As it turned out, the alkylation of these compounds proceeds under the action of various reactants in the presence of potassium carbonate in DMF with the formation of 6-O-alkyl derivatives **4a-l** in high yield.



4a,**d**,**e**,**g**,**j–l**, **5b**, **6b** R = H, **4 b**, **c**, **f**, **h**, **5a**, **e**, **6a**, **7a** R = Me, **4 i**, **5c**, **d**, **7 b** R = Ph, **4a–c**, **5a**, **7a** R^3 = benzofuryl-2,
4d–j, **5b–e**, **6a**,**b**, **7b** R^3 = 7-methoxybenzofuryl-2, **4 k**, **l** R^3 = 5-bromobenzofuryl-2, **4 a**,**d**,**k** R^4 = Me, **b**, **e**, **f** R^4 = Et;
c, **g–i**, **l** $R^4 = CH_2CO_2Et$; **j** $R^4 = CH_2CH{=}CMe_2$; **5 a**, **c** R^5 = furyl-2, **b** R^5 = thienyl-2; **d** R^5 = Ph; **e** R^5 = 3,4-$OCH_2OC_6H_3$;
6 a R^6 = Me, **b** R^6 = 4-$MeOC_6H_4$, **7 a** $R^7 = R^8$ = Me, **b** $R^7R^8 = CH_2CH_2OCH_2CH_2$

Acylation of compounds **3b-e** was effected on extended exposure of the initial 4-(2-benzofuryl)-6-hydroxycoumarins to the acid chlorides of carboxylic and sulfonic acids, and also to dialkylcarbamoyl-chlorides with the formation of the corresponding derivatives **5a-e, 6a,b, and 7a,b**.

TABLE 1. Characteristics of 2-(4-Benzofuryl)coumarins **3-7**

Compound	Empirical formula	Found, % / Calculated, %			mp, °C	Yield, %
		C	H	Br (S) [N]		
3a	$C_{17}H_{10}O_4$	73.56 / 73.38	3.48 / 3.62		262-263	56
3b	$C_{18}H_{12}O_4$	73.82 / 73.97	4.26 / 4.14		265-267	47
3c	$C_{18}H_{12}O_5$	70.25 / 70.13	3.86 / 3.92		271-273	65
3d	$C_{19}H_{14}O_5$	70.68 / 70.80	4.26 / 4.38		310-312	57
3e	$C_{24}H_{16}O_5$	75.21 / 74.99	4.04 / 4.20		288-290	56
3f	$C_{20}H_{16}O_5$	71.25 / 71.42	4.96 / 4.80		249-251	43
3g	$C_{17}H_9BrO_4$	57.28 / 57.17	2.81 / 2.54	22.09 / 22.37	290-292	39
4a	$C_{18}H_{12}O_4$	73.67 / 73.97	4.25 / 4.14		165-167	78
4b	$C_{20}H_{16}O_4$	74.74 / 74.99	5.13 / 5.03		206-208	82
4c	$C_{22}H_{18}O_6$	69.67 / 69.84	4.95 / 4.80		148-150	68
4d	$C_{19}H_{14}O_5$	71.03 / 70.80	4.24 / 4.38		223-224	86
4e	$C_{20}H_{16}O_5$	71.35 / 71.42	4.68 / 4.80		156-167	74
4f	$C_{21}H_{18}O_5$	72.14 / 71.99	4.98 / 5.18		190-191	67
4g	$C_{22}H_{18}O_7$	66.84 / 67.00	4.67 / 4.60		159-161	80
4h	$C_{23}H_{20}O_7$	67.52 / 67.64	5.06 / 4.94		219-220	77
4i	$C_{28}H_{22}O_7$	71.32 / 71.48	4.62 / 4.71		198-200	73
4j	$C_{23}H_{20}O_5$	73.26 / 73.39	5.06 / 5.36		155-156	77
4k	$C_{18}H_{11}BrO_4$	58.33 / 58.25	3.18 / 2.99	21.25 / 21.53	233-234	83
4l	$C_{21}H_{15}BrO_6$	56.68 / 56.91	3.41 / 3.41	18.18 / 18.03	143-144	75
5a	$C_{23}H_{14}O_6$	71.24 / 71.50	3.67 / 3.65		204-205	67
5b	$C_{23}H_{14}O_6S$	65.81 / 66.02	3.45 / 3.37	(7.38) / (7.66)	235-237	65
5c	$C_{29}H_{18}O_7$	72.65 / 72.80	3.87 / 3.79		272-274	53
5d	$C_{31}H_{20}O_6$	76.01 / 76.22	4.25 / 4.13		233-234	78
5e	$C_{27}H_{18}O_8$	69.16 / 68.94	3.92 / 3.86		237-239	83
6a	$C_{20}H_{16}O_7S$	59.73 / 59.99	3.82 / 4.03	(8.33) / (8.01)	215-216	76
6b	$C_{25}H_{18}O_8S$	62.68 / 62.76	3.92 / 3.79	(6.95) / (6.70)	161-162	81
7a	$C_{21}H_{17}NO_5$	69.27 / 69.41	4.93 / 4.72	[4.01] / [3.85]	190-191	87
7b	$C_{29}H_{23}NO_7$	69.83 / 70.01	4.71 / 4.66	[2.66] / [2.82]	198-199	68

TABLE 2. ^{1}H NMR Spectra of 4-(2-Benzofuryl)coumarins **3-7**

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)									
	Coumarin residue					Benzofuran residue				
	H-3 (s)	H-5	6-R	7-R	H-8	H-3' (s)	H-4' (m)	H-5' (m)	H-6' (m)	7'-R
1	2	3	4	5	6	7	8	9	10	11
3a	6.88	7.66 (d, *J* = 2.8)	9.86 (1H, s)	7.13 (dd, *J* = 2.6, *J* = 9.0)	7.75 (d, *J* = 9.0)	7.80	7.82	7.38	7.50	7.36 (m)
3b	6.78	7.25 (s)	9.81 (1H, s)	2.25 (3H, s)	7.67 (s)	7.72	7.82	7.39	7.51	7.74 (m)
3c	6.82	7.60 (d, *J* = 2.6)	9.88 (1H, s)	7.14 (dd, *J* = 2.6, *J* = 9.0)	7.36 (d, *J* = 9.0)	7.75	7.33	7.29	7.09	4.01 (3H, s)
3d	6.73	7.59 (s)	9.82 (1H, s)	2.25 (3H, s)	7.28 (s)	7.69	7.37	7.30	7.10	4.01 (3H, s)
3e	6.80	7.73 (s)	10.05 (1H, s)	7.47, 7.68 (5H, m)	7.42 (s)	7.78	7.37	7.30	7.10	4.01 (3H, s)
3f	6.71	7.51 (s)	9.79 (1H, s)	2.25 (3H, s)	7.27 (s)	7.66	7.07	7.26	7.35	1.43 (3H, t, *J* = 7); 4.29 (2H, q, *J* = 7)
3g	6.87	8.02 (d, *J* = 2.5)	9.87 (1H, s)	7.14 (dd, *J* = 2.5, *J* = 9.0)	7.35 (d, *J* = 8.6)	7.73	7.73	–	7.62	7.58 (m)
4a	6.92	7.72 (d, *J* = 2.9)	3.88 (3H, s)	7.34 (dd, *J* = 2.9, *J* = 9.0)	7.47 (d, *J* = 9.0)	7.92	7.82	7.38	7.50	7.77 (m)
4b	6.84	7.62 (s)	1.40 (3H, t, *J* = 7.0); 4.14 (2H, q, *J* = 7.0)	2.29 (3H, s)	7.36 (s)	7.90	7.82	7.39	7.49	7.76 (m)
4c	6.85	7.58 (s)	1.13 (3H, t, *J* = 7.0); 4.16 (2H, q, *J* = 7.0); 4.98 (2H, s)	2.35 (3H, s)	7.39 (s)	7.86	7.81	7.39	7.52	7.74 (m)
4d	6.90	7.76 (d, *J* = 2.9)	3.88 (3H, s)	7.34 (dd, *J* = 2.9, *J* = 8.5)	7.47 (d, *J* = 8.5)	7.90	7.36	7.29	7.10	4.01 (3H, s)
4e	6.88	7.72 (d, *J* = 2.8)	1.38 (3H, t, *J* = 7.0); 4.13 (2H, q, *J* = 7.0)	7.30 (dd, *J* = 2.8, *J* = 8.0)	7.44 (d, *J* = 8.0)	7.88	7.35	7.28	7.09	4.00 (3H, s)
4f	6.82	7.72 (s)	1.42 (3H, t, *J* = 7.0); 4.17 (2H, q, *J* = 7.0)	2.29 (3H, s)	7.32 (s)	7.86	7.36	7.29	7.09	4.01 (3H, s)
4g	6.90	7.72 (d, *J* = 3.0)	1.17 (3H, t, *J* = 7.0); 4.17 (2H, q, *J* = 7.0); 4.93 (2H, s)	7.36 (dd, *J* = 3.0, *J* = 9.0)	7.48 (d, *J* = 9.0)	7.87	7.35	7.29	7.10	4.01 (3H, s)
4h	6.81	7.61 (s)	1.13 (3H, t, *J* = 7.0); 4.16 (2H, q, *J* = 7.0); 4.94 (2H, s)	2.35 (3H, s)	7.38 (s)	7.83	7.35	7.30	7.10	4.01 (3H, s)
4i	6.89	7.88 (s)	1.11 (3H, t, *J* = 7.0); 4.15 (2H, q, *J* = 7.0); 4.95 (2H, s)	7.47, 7.71 (5H, m)	7.50 (s)	7.78	7.35	7.30	7.10	4.01 (3H, s)

TABLE 2 (continued)

1	2	3	4	5	6	7	8	9	10	11
4j	6.88	7.72 (d, J = 3.0)	1.70 (3H, s), 1.74 (3H, s), 4.64 (2H, m), 5.46 (1H, m)	7.32 (dd, J = 3.0, J = 9.0)	7.45 (d, J = 9.0)	7.86	7.36	7.29	7.10	4.00 (3H, s)
4k	6.90	7.64 (d, J = 2.7)	3.86 (3H, s)	7.32 (dd, J = 2.7, J = 9.0)	7.44 (d, J = 9.0)	7.82	7.99	—	7.60	7.73 (m)
4l	6.93	7.64 (d, J = 2.8)	1.17 (3H, t, J = 7.0); 4.18 (2H, q, J = 7.0); 4.92 (2H, s)	7.36 (dd, J = 2.8, J = 9.0)	7.47 (d, J = 9.0)	7.82	8.00	—	7.63	7.73 (m)
5a	6.93	8.18 (s)	6.84 (1H, m); 7.65 (1H, m); 8.14 (1H, m)	2.29 (3H, s)	7.54 (s)	7.93	7.79	7.36	7.48	7.74 (m)
5b	6.95	8.18 (d, J = 2.5)	7.69 (1H, m); 8.07 (1H, m); 8.13 (1H, m)	7.34 (dd, J = 2.5, J = 9.0)	7.62 (d, J = 9.0)	7.93	7.34	7.27	7.08	3.98 (3H, s)
5c	6.95	8.27 (s)	6.75 (1H, m); 7.51 (1H, m); 8.05 (1H, m)	7.43, 7.60 (5H, m)	7.67 (s)	7.95	7.35	7.27	7.08	4.00 (3H, s)
5d	6.96	8.29 (s)	4.40 (3H, m); 7.60 (5H, m); 8.02 (2H, m)	4.40 (3H, m); 7.60 (5H, m); 8.02 (2H, m)	7.68 (s)	7.95	7.34	7.27	7.08	3.97 (3H, s)
5e	6.88	8.09 (s)	6.20 (2H, s); 7.14 (1H, m); 7.61 (1H, m); 7.81 (1H, m)	2.27 (3H, s)	7.53 (s)	7.89	7.33	7.26	7.07	3.97 (3H, s)
6a	6.95	8.26(s)	3.59 (3H, s)	2.43 (3H, s)	7.55 (s)	7.85	7.35	7.29	7.10	3.99 (3H, s)
6b	6.95	7.75 (d, J = 2.8)	3.66 (3H, s); 7.08 (2H, d, J = 9.1); 7.79 (2H, d, J = 9.1)	7.44 (dd, J = 2.8; J = 9.0)	7.56 (d, J = 9.0)	7.56	7.36	7.32	7.13	4.03 (3H, s)
7a	6.90	7.88 (s)	2.94 (3H, s); 3.12 (3H, s)	2.26 (3H, s)	7.46 (s)	7.95	7.82	7.38	7.50	7.76 (m)
7b	6.91	8.07 (s)	3.25 (2H, m); 3.48 (6H, m)	7.51 (5H, m)	7.88 (s)	7.56	7.36	7.28	7.09	4.00 (3H, s)

We have therefore shown that the selective alkylation of the phenolic hydroxyl of salicylic aldehydes by the action of 4-chloromethyl-6-hydroxycoumarins with subsequent intramolecular cyclization makes possible the synthesis of derivatives of 4-(2-benzofuryl)-6-hydroxycoumarin, without previous protection of the hydroxyl group of the alkylating agent. The alkylation and acylation of the synthesized benzofuryl-substituted 6-hydroxycoumarins have been investigated.

EXPERIMENTAL

A check on the progress of reactions and an assessment of the purity of the obtained compounds was effected by TLC on Silufol UV-254 and Merck 60 F_{254} plates. Chloroform–methanol mixtures, 9:1, 95:5, and also hexane–ethyl acetate, 1:2, were used as eluent. The ^{1}H NMR spectra were measured on a Varian VXR 300 (300 MHz) instrument in DMSO-d_6, internal standard was TMS.

Synthesis of 4-Chloromethylcoumarins 1a-c [6]. A mixture of 4-chloroacetoacetic ester (100 mmol) and the appropriate (un)substituted hydroquinone (100 mmol) was poured into 73% sulfuric acid (50 ml) and the mixture stirred at room temperature for 18-24 h. The reaction mixture was poured onto ice, the precipitated solid filtered off, and crystallized from dioxane.

4-Chloromethyl-6-hydroxycoumarin (1a). Yield 47%; mp 220-222°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.97 (2H, s, 4-CH_2); 6.33 (1H, s, H-3); 7.09 (1H, dd, *J* = 8.6, *J* = 2.2, H-7); 7.15 (1H, d, *J* = 2.2, H-8); 7.30 (1H, d, *J* = 8.6, H-5); 9.86 (1H, s, 6-OH). Found, %: Cl 16.56. $C_{10}H_7ClO_3$. Calculated, %: Cl 16.83.

4-Chloromethyl-6-hydroxy-7-methylcoumarin (1b). Yield 56%; mp 223-225°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.21 (3H, s, 7-CH_3); 4.91 (2H, s, 4-CH_2); 6.58 (1H, s, H-3); 7.11 (1H, s, H-8); 7.21 (1H, s, H-5); 9.82 (1H, s, 6-OH). Found, %: Cl 16.03. $C_{11}H_9ClO_3$. Calculated, %: Cl 15.78.

4-Chloromethyl-6-hydroxy-7-phenylcoumarin (1c). Yield 53%; mp 234-235°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 4.97 (2H, s, 4-CH_2); 6.68 (1H, s, H-3); 7.31 (1H, s, H-8); 7.37 (1H, s, H-5); 7.39-7.47 (5H, m, 7-C_6H_5); 10.06 (1H, s, 6-OH). Found, %: Cl 12.54. $C_{16}H_{11}ClO_3$. Calculated, %: Cl 12.37.

Preparation of 4-(2-Benzofuryl)-6-hydroxycoumarins 3a-g (General Method). Potassium carbonate (40 mmol) was added to a solution of the appropriate salicylaldehyde **2a-d** (10 mml) in DMF (20 ml). The mixture was stirred and heated to 60-80°C and the appropriate 4-chloromethyl-6-hydroxycoumarin **1a-c** (10 mmol) was added. The reaction mixture was maintained for 8 h at 100°C (the end of the reaction was determined by TLC). After cooling, the reaction mixture was poured into cold water (100 ml), the mixture was acidified to pH 4 with dilute H_2SO_4, the solid was filtered off, and crystallized from DMF.

Preparation of 6-Alkoxy-4-(2-benzofuryl)coumarins 4a-l (General Method). Freshly calcined potassium carbonate (4.1 g, 30 mmol) was introduced into a hot solution of the appropriate 6-hydroxycoumarin **3a-e** (10 mmol) in DMF (30 ml), and then the appropriate alkyl halide or dialkyl sulfate (12 mmol) was added with stirring and heating to 60-80°C. The reaction mixture was maintained for 1-4 h (the end of the reaction was determined by TLC) and then poured into acidified ice-water (100 ml). The precipitated solid was filtered off and crystallized from ethanol.

Preparation of 6-Acyloxy-4-(2-benzofuryl)coumarins 5a-e, 6a,b, and 7a,b (General Method). The acid chloride (12 mmol) was added to a solution of the appropriate 6-hydroxycoumarin **3b-e** (10 mmol) in the minimum quantity of absolute pyridine. The reaction mixture was maintained at room temperature for 1 day (the end of the reaction was determined by TLC), then poured into ice-water. The precipitated solid was filtered off and crystallized from a suitable solvent.

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