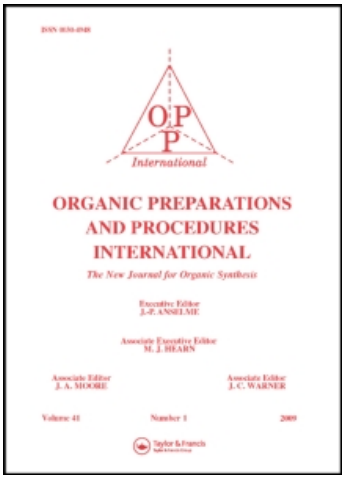

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SYNTHESIS OF 6-HALO-1,2-BENZISOXAZOLES, CHROMENO-6,7-ISOXAZOLES AND CHROMENO-6,7-OXAZOLES

Lenuta Cires[a]; Harry Ofenberg[a]; Cotinica Craita[a]
[a] "Al. I. Cuza" University, Faculty of Chemistry, Iasi-6, ROMANIA

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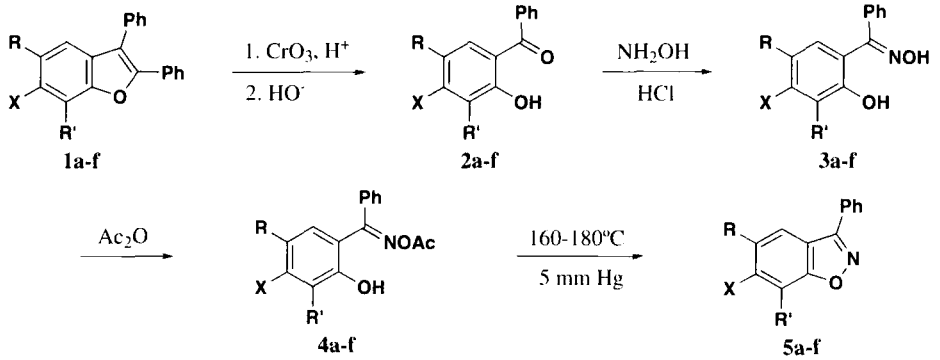
SYNTHESIS OF 6-HALO-1,2-BENZISOXAZOLES, CHROMENO-6,7-ISOXAZOLES AND CHROMENO-6,7-OXAZOLES

Submitted by (04/18/00) Lenuta Cires*, Harry Ofenberg and Cotinica Craita

"Al. I. Cuza" University, Faculty of Chemistry
Bd Carol I, No. 11 R-6600 Iasi-6, ROMANIA

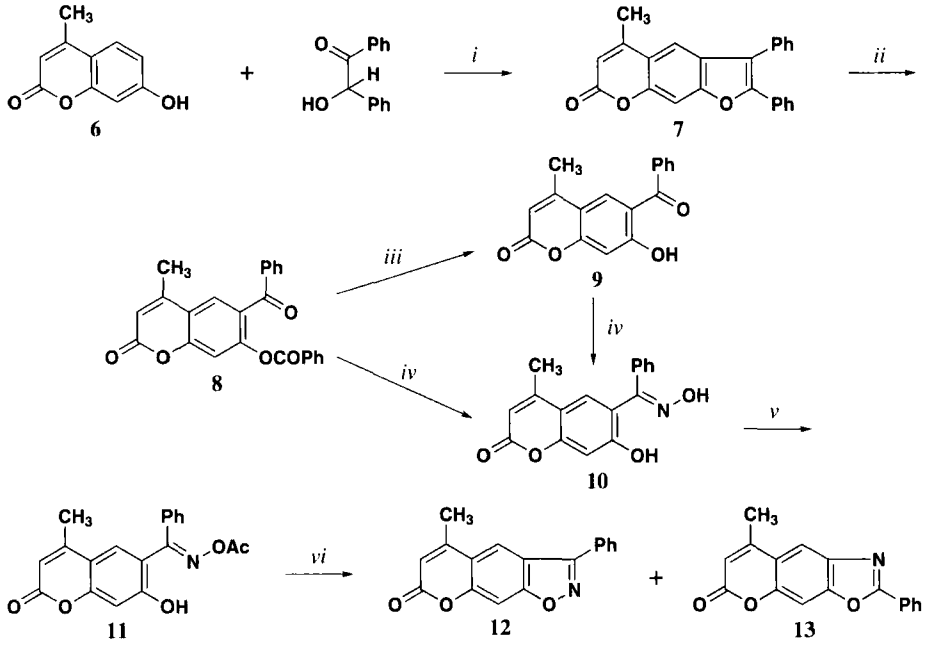
6-Substituted benzisoxazoles have been developed as potent and selective inhibitors of the enzyme acetylcholinesterase.[1] In addition, some of these 1,2-benzisoxazoles are biologically active displaying antitubercular and antifungal activity.[2] Consequently, the development of synthetic methods for the elaboration of suitably substituted 1,2-benzisoxazole derivatives constitutes an area of current interest. Moreover, 6-substituted-1,2-benzisoxazoles can be only obtained by cyclization, since electrophilic substitution of 1,2-benzisoxazoles affords 5- or 7-substituted derivatives.[3,4] The presence of a halogen at position 6 of 3-phenyl-1,2-benzisoxazole would allow access to models displaying an array of promising chemical and physical properties. We now report the preparation of 6-halo-3-phenyl-1,2-benzisoxazoles **5a-f** (*Scheme 1*) as well as the conversion of furocoumarin **7** to



a) R, R' = H, X = Br; b) R = CH_3, R' = H, X = Br; c) R = H, R' = CH_3, X = Br;
d) R = H, R' = H, X = I; e) R = CH_3, R' = H, X = I; f) R = H, R' = CH_3, X = I.

Scheme 1

the corresponding izoxazole **12** and oxazole **13** (*Scheme 2*).



i) $B(OH)_3$, 180-200°C *ii*) CrO_3, H^+ *iii*) HO^- *iv*) NH_2OH/HCl, pyridine:ethanol (1:10) *v*) $(CH_3CO)_2O$/ethanol *vi*) 180-190°C, 0.1 mm Hg or Δ in pyridine.

Scheme 2

1a-f[5] with hydroxylamine hydrochloride afforded the 2-hydroxybenzophenone oximes (**3a-f**), which upon treatment with acetic anhydride at room temperature led to the corresponding 2-hydroxybenzophenone O-acetyl oximes (**4a-f**). It should noted that if the acetylation reaction is performed with heating, the diacetyl derivatives of oximes **3a-f** are obtained in good yields.

Two general methods for the synthesis of *linear* furocoumarins are known. The first consists of construction of the α–pyrone ring onto a benzo[b]furan derivative[6] and the second is by elaboration of the furan ring onto a coumarin ring.[7] Although it has been previously reported that 7-hydroxybenzopyran-2-one does not undergo condensation reaction with benzoin in the presence of *p*-toluenesulfonic acid (PTS),[8] compound **7** has now been obtained by the condensation of 7-hydroxy-4-methylbenzopyran-2-one (**6**) with benzoin in the presence of boric acid for 2h at 180-200°.[9] The NMR spectrum of **7** supported the assignment of the linear structure; its ^{1}H-NMR spectrum shows two singlets at δ 7.62 and 7.50 corresponding to H-5, H-8 aromatic protons (Table 2). A small amount of the angular isomer was detected by ^{1}H-NMR too. The conversion of furocoumarin **7** to chromenoisoxazole **12** and chromenooxazole **13** is shown in Scheme 2.

As shown in Scheme 2, oxime **10** can be obtained from compound **8** either a) by direct treatment with a solution of hydroxylamine hydrochloride in a 10:1 mixture of ethanol and pyridine or b) alternatively by alkaline hydrolysis of **8** to **9**[10] followed by treatement with hydroxylamine as mentioned before; the yield of 10 was by the direct method twice as large. The configuration of the

oximes and O-acetyl derivatives is important to the course of the subsequent cyclization because of the reaction mechanism. Although the action of alkali generally opens the pyrone ring, the original coumarin is regenerated upon the acidification.

The NMR spectra of all the oximes (**3a-f** and **10**) and of the O-acetyl derivatives (**4a-f** and **11**) indicate that there is only one isomer present. The IR spectrum of **3a-f** and **10** indicated fairly sharp absorption bands for the OH oxime group at 3300-3400 cm^{-1}, while absorption band of phenolic group is relatively broad around 3200- 3400 cm^{-1}. The IR spectra of the corresponding oxime acetates (**4a-f** and **11**) indicated a similar broad band of phenolic group which is characteristic of a strong hydrogen bond. Furthermore, the frequency and the intensity of the associated bands are a measure of the strength of the hydrogen bond. Based on previous studies on some similar oximes[10] as well as IR spectral data presented above, the (***E***) configuration is assigned to all oximes and their O-acetyl derivatives.

Table 1. Physical Data of Synthesized Compounds

Cmpd.	Yield (%)	mp. (^{0}C)	Elemental Analysis Calcd (Found) C	H	N	X
3a	75	115	53.45 (53.39)	3.45 (3.36)	4.79 (4.81)	27.35 (27.01)
3b	78	135-137	54.92 (54.68)	3.95 (3.92)	4.58 (4.43)	26.10 (26.28)
3c	69	140-142	54.92 (54.74)	3.95 (3.89)	4.58 (4.51)	26.10 (26.31)
3d	82	143-144	46.04 (45.92)	2.97 (2.92)	4.13 (3.93)	37.42 (37.30)
3e	85	152-155	47.61 (47.58)	3.42 (3.37)	3.97 (4.08)	35.93 (35.69)
3f	83	161	47.61 (47.60)	3.42 (3.39)	3.97 (3.90)	35.93 (35.75)
4a	80	117	53.91 (53.85)	3.62 (3.64)	4.19 (4.24)	23.91 (23.83)
4b	85	129-130	55.19 (54.91)	4.05 (3.98)	4.02 (4.12)	22.95 (22.65)
4c	82	148-150	55.19 (55.08)	4.05 (4.11)	4.02 (3.96)	22.95 (22.78)
4d	87	75	47.27 (47.33)	3.17 (3.21)	3.67 (3.59)	33.29 (33.13)
4e	84	143	48.63 (48.50)	3.57 (3.40)	3.54 (3.61)	32.11 (31.97)
4f	87	136-138	48.63 (48.58)	3.57 (3.47)	3.54 (3.48)	32.11 (32.02)
5a	64	110-112	56.96 (57.02)	2.94 (2.81)	5.11 (5.02)	29.15 (28.98)
5b	68	114-116	58.36 (58.15)	3.50 (3.52)	4.86 (4.78)	27.73 (27.53)
5c	69	118-120	58.36 (58.08)	3.50 (3.36)	4.86 (4.93)	27.73(27.68)
5f	71	112	48.62 (48.39)	2.51 (2.55)	4.36 (4.30)	39.52 (39.47)
5e	75	128-130	50.17 (49.95)	3.01 (3.15)	4.18 (3.95)	37.87 (37.91)
5f	75	104-105	50.17 (49.89)	3.01 (2.98)	4.18 (4.06)	37.87 (37.69)
7	59	225-226	81.80 (81.72)	4.58 (4.51)	-	-
8	90	278-280	74.99 (74.85)	4.20 (3.90)	-	-
9	80	178-180	72.85 (72.68)	4.32 (4.11)	-	-
10	80	264-265	69.15 (69.00)	4.44 (4.41)	4.74 (4.65)	-
11	81	184	67.65 (67.54)	4.48 (4.51)	4.15 (4.07)	-
12	60	213-214	73.64 (73.71)	4.00 (4.01)	5.05 (4.94)	-
13	20	232-233	73.64 (73.61)	4.00 (4.02)	5.05 (4.94)	-

Table 2. Spectroscopic Data of Compounds **3a-f**, **4a-f** and **5a-f**.

Cmpd	IR (cm^{-1})	^{1}H-NMR (δ)	MS (m/e)
3a	3400 and 3397 (N-OH, OH), 1627 (C=N), 1599	6.71 (*d*, 1H, ^3J = 8.2Hz, H_6), 6.95 (*dd*, 1H, *J* = 8.2Hz, *J* = 1.8Hz, H_5), 7.11 (*d*, 1H, *J* = 1.8Hz, H_3), 7.3 (*m*, 2H, $H_{Ph.}$), 7.45 (*m*, 3H, $H_{Ph.}$), 11.4 (*s*, N-OH), 11.7 (*s*, 1H, OH)	291 (M^+, 9), 275 (M^+ -OH, 17), 247 (44), 166 (51), 104 (70), 77 (100)
3b	3360 (NOH, OH), 1610 (C=N), 1580	2.19 (*s*, 3H, CH_3), 6.67 (*s*, 1H, H_6), 7.34 (*m*, 3H, H_3, H_{Ph}), 7.56 (*m*, 3H, H_{Ph}), 11.2 (br *s*, 2H, NOH, OH)	-
3c	3300 (N-OH, OH), 1650 (C=N), 1580	2.4 (s, 3H, CH_3), 6.55 (*d*, 1H, *J* = 8.2Hz, H_6), 6.94 (*d*, 1H, *J* = 8.2Hz, H_5), 7.32 (*m*, 2H, $H_{Ph.}$), 7.52 (*m*, 3H, $H_{Ph.}$), 11.6 (br *s*, 1H, N-OH, OH)	-
3d	3345 and 3400 (N-OH), OH), 1628 (C=N)	6.55 (*d*, 1H, *J* = 8.3 Hz, H_6), 7.15 (*d*, 1H, *J* = 8.3 Hz, H_5), 7.28 (*s*, 1H, H_3), 7.35 (m, 2H, H_{Ph}), 7.45 (m, 3H, H_{Ph}), 11.3 (s, 1H, N-OH), 11.68 (*s*, OH)	339 (M^+, 22), 322 (25), 293 (31), 166 (60), 77 (100)
3e	3320-3300 (OH, N-OH), 1630 (C=N), 1590	2.13 (*s*, 3H, CH_3), 6.57 (*s*, 1H, H_6), 7.30 (*m*, 2H, $H_{Ph.}$), 7.45 (*m*, 4H, H_{Ph}), 10.89 (br *s*, 2H, OH, NOH)	353 (M^+, 25), 336 (29), 335 (100)
3f	3400-3340 (OH, N-OH), 1620 (C=N), 1597	2.45 (*s*, 3H, CH_3), 6.35 (*d*, 1H, *J* = 8.1Hz, H_6), 7. 23 (*d*, 1H, *J* = 8.1Hz, H_5), 7.3 (*m*, 2H, $H_{Ph.}$), 7.5 (*m*, 3H, $H_{Ph.}$), 11.3 (br *s*, N-OH), 11.7 (br *s*, OH);	354 (MH^+, 35), 336 (M^+-H_2O,100), 237 (16), 227 (12)
4a	3400 (N-OH), 1630 (C=N), 1776 (C=O)	2.1 (*s*, 3H, CH_3), 7.1 (*s*, 3H), 7.4 (*m*, 2H, $H_{Ph.}$), 7.5 (*m*, 3H, $H_{Ph.}$), 10.75 (br *s*, OH)	334 (MH^+, 60), 321 (29), 290 (43), 77 (100)
4b	3400 (OH), 1780 (C=O), 1615 (C=N), 1600	2.04 (*s*, 3H, CH_3), 2.42 (*s*, 3H, $COCH_3$), 6.68 (*s*, 1H, H_6), 7.36 (*m*, 3H, H_3, H_{Ph}), 7.57 (*m*, 3H, $H_{Ph.}$), 11.2 (br s, OH)	-
4c	1680 (C=O), 1620 (C=N)	2.02 (*s*, 3H, $COCH_3$), 2.39 (*s*, 3H, CH_3), 6.57 (*d*, 1H, *J* = 8.3Hz, H_6), 7.19 (*d*, 1H, *J* = 8.3Hz, H_5), 7.29 (*m*, 2H, H_{Ph}), 7.79 (*m*, 3H, H_{Ph}), 11.71 (br s, OH)	-
4d	3400 (OH), 1772 (C=O), 1628 (C=N), 1597	2.05 (*s*, 3H,CH_3), 6.8 (*d*, 1H, H_6), 7. 23 (*d*, 1H, H_5), 7.3 (*s*, 1H, H_3), 7.48 (*m*, 2H, $H_{Ph.}$), 7.6 (*m*, 3H, $H_{Ph.}$), 10.7 (s, 1H, OH)	381 (M^+, 59), 336 (15), 321 (45), 77 (100), 63 (80)
4e	3400 (OH), 1775 (C=O), 1620 (C=N), 1600	2.06 (*s*, 3H, CH_3), 2.36 (*s*, 3H, $COCH_3$), 6.38 (*s*, 1H, 6-H), 7.38 (*m*, 3H, H_3, H_{Ph}), 7.57 (*m*, 3H, H_{Ph}), 11.68 (br *s*, OH)	395 (M^+, 36), 335 (100), 208 (21)
4f	1680 (C=O), 1580 (C=N)	2.04 (*s*, 3H, $COCH_3$), 2.48 (*s*, 3H, CH_3), 6.38 (*d*, 1H, *J* = 8.4 Hz, 6-H), 7.24 (*d*, 1H, *J* = 8.4 Hz, H_5), 7.27 (*m*, 2H, H_{Ph}), 7.50 (*m*, 3H, $H_{Ph.}$), 11.71 (s, OH)	395 (M^+, 40), 364 (13), 335 (100), 210 (39), 209 (40)

Table 2. Continued...

Cmpd	IR (cm^{-1})	^{1}H-NMR (δ)	MS (m/e)
5a	1603 (C=CAr)	7.63 (*m*, 3H, H_{Ph}), 7.68 (*d*, 1H, *J* = 8.3 Hz, H_5), 8.05 (*m*, 2H, H_{Ph}), 8.1 (*d*, 1H, *J* = 8.3Hz, H_4), 8.25 (s, 1H, H_7)	276 (MH^+, 100), 275 (M^+, 90), 196 (73), 94
5b	1598 (C=CAr)	2.51 (s, 3H,CH_3), 7.56 (*m*, 3H, H_{Ph}), 7.73 (*s*, 1H,), 7.89 (*d*, 1H), 7.92 (*m*, 2H, H_{Ph})	-
5c	1596 (C=CAr)	2.65 (s, 3H, CH_3), 7.45 (*d*, 1H, *J* = 8.4 Hz, H_5) 7.6(*m*, 3H, H_{Ph}), 7.8 (*d*, 1H, *J* = 8.4 Hz, H_4), 7.98 (*m*, 2H, $H_{Ph.}$)	-
5d	1597 and 1573 ($C=C_{arom.}$)	7.6 (m, 3H, $H_{Ph.}$), 7.75 (d, 1H, *J* = 8.3 Hz, H_5), 7.88 (*d*, 1H, *J* = 8.3 Hz, H_4), 7.98 (*m*, 2H, H_{Ph}), 8.38 (br *s*, 1H, *J* = 1.3 Hz, H_7)	276 (MH^+, 100), 275 (M^+, 90), 196 (15), 196 (73)
5e	1603 (C=CAr)	2.45 (s, 3H, CH_3), 7.50 (*m*, 4H, H_4, $H_{Ph.}$), 8.20 (*m*, 3H, H_7, $H_{Ph.}$)	335 (M^+, 100), 210 (40)
5f	1597 (C=CAr)	2.67 (s, 3H, CH_3), 7.43 (*d*, 1H, *J* = 8.5 Hz, H_5), 7.52 (*m*, 3H, H_{Ph}), 7. 77 (*d*, 1H, *J* = 8.5 Hz, H_4), 7.92 (*m*, $2H_{Ph}$)	335 (M^+, 100), 210 (40)

From among the methods known for the conversion of oximes to benzisoxazoles, the most common is the Lindemann's pyrolysis of 2-hydroxybenzophenonacetoximes.[11]

Table 3. Spectroscopic Data of Compounds **7-13**.

Cmpd	IR (cm^{-1})	^{1}H-NMR (δ)	^{13}C-NMR (δ)
7	1770 (C=O), 1580	7.64-7.60 (m, 3H, $2H_{Ph}$, H_4), 7.47-7.53 (m, 6H, H_9, $5H_{Ph}$), 7.33-7.31 (m, 3 H_{Ph}), 6.28 (d, 1H, J =1.0 Hz, H_6), 2.47 (d, 3H, J = 0.9 Hz, CH_3)	161.05 (C_7), 155.3 (C_3), 152.7 (C_2), 152.3 (C_{9a}), 151.9 (C_{2a}), 131.9, 129.7, 129.6, 129.3, 128.9, 128.5, 128.2, 127.7, 126.9, 116.9 (C_{3a}), 116.7 (C_{5a}),115.1 (C_4), 113.3(C_6), 99.5 (C_9), 19.2 (CH_3)
8	3056, 1746 (C=O), 1626 (C=O), 1597, 1450	2.43 (s, 3H, J = 1.2 Hz, CH_3), 6.33 (s, 1H, C_3, J = 1.2 Hz), 7.29-7.38 (m, 5H, 4 H_{Ph}, H_8), 7.43-7.53 (m, 2 H_{Ph}), 7.70-7.76 (m, 4 H_{Ph}), 7.88 (s, 1H, H_5, J = 2 Hz)	193.3 (C=O), 163.8 (C=O), 159.7, 155.5, 151.7, 151.1, 137.3, 133.8, 133.2, 130.0 129.5, 128.5, 128.4, 128.3, 127.9, 127.1, 117.8, 115.2, 111.9, 77.3, 77.0, 76.7, 18.7
9	1655 (C=O), 1744 (C=O)	12.36 (s, 1H, OH), 7.85 (s, 1H, H_5), 7.69-7.65(m, $2H_{Ph}$), 7.64-7.62 (m, 1 H_{Ph}), 7.56-7.52 (m, $2H_{Ph}$), 6.98 (s, 1H, H_8), 6.19 (s, 1H, H_3), 2.25 (s, 3H, CH_3), 12.36 (s, 1H, OH)	200.3 (C=O), 165.9 (C_7), 159.0 (C_2), 151.9 (C_{8a}), 137.2 (C_{Ph}), 132.6 (C_{Ph}), 131.2(C_5), 129.1 (C_{Ph}), 128.6 (C_{Ph}), 116.3 (C_6), 112.8 (C_3), 112.6 (C_{4a}) 105.3 (C_8), 18.4 (CH_3)
10	3251 (N-OH, OH), 1699 (C=O), 1597	11.70 (s, N-OH), 11.65 (s, OH), 7.49 - 7.31 (m, 5 H_{Ph}), 7.22 (s, H_3), 6.81 (s, H_8), 6.13 (s, H_5, J = 1.2 Hz), 2.14 (d, CH_3, J = 1.0 Hz)	160.7 (C_2), 160.2 (C_9), 156.6 (C_{8a}), 154.9 (C_{4a}), 153.2 (C_4), 132.2 (C_{Ph}), 129.3 (C_{Ph}), 129.1 (C_{Ph}), 128.5 (C_{Ph}), 127.1 (C_3), 119.4 (C_7), 112.2 (C_6), 111.5 (C_5), 103.6 (C_8), 18.1 (CH_3)

Table 3. Continued...

Cmpd	IR (cm^{-1})	^{1}H-NMR (δ)	^{13}C-NMR (δ)
11	2798, 1784 (C=O), 1633 (C=O), 1619 (C=N), 1590	11.75 (*s*, 1H, OH), 7.56-7.60 (*m*, 3H, H_{Ph}), 7.28-7.37 (*m*, 2H, H_{Ph}), 7.09 (*s*, 1H, H_3), 6.95 (*s*, 1H, H_8), 6.06 (*t*, 1H, H_5), 2.08 (*s*, 6H, $2CH_3$)	166.7 (C=O), 165.3 (C_2), 162.1 (C_{4a}), 160.4 (C=N), 156.3 (C_{8a}), 151.8 (C_4), 130.2 (C_{Ph}), 129.9 (C_{Ph}), 128.6 (C_8), 128.5 (C_{Ph}) 128.1(C_{Ph}), 115.2 (C_7), 112.7 (C_6), 112.2 (C_5), 105.1 (C_3), 18.9 (CH_3), 18.1 (CH_3)
12	3059, 1728 (C=O), 1585	8.11 (*s*, H_4), 7.97-7.95 (m, 2H, H_{Ph}), 7.64-7.58 (m, 4H, H_9, 3 H_{Ph}), 6.36 (d, 1H, H_6, J = 0.8 Hz), 2.56 (d, 3H, J = 1.2 Hz, CH_3)	164.3 (C(3)), 159.9 (C_7), 157.4 (C_{9a}), 154.8 (C_{8a}), 151.8 (C_5), 130.7 (C_{Ph}), 129.3 (C_{Ph}), 127.9 (C_{Ph}), 127.8 (C_{Ph}), 118.4 (C_{4a}), 117.8 (C_4), 114.3 (C_6), 97.9 (C_9), 19.1 (CH_3)
13	3039, 1708 (C=O), 1633, 1594	8.11 (*s*, H_4), 7.97-7.95 (m, 2H, H_{Ph}), 7.64-7.58 (m, 4H, H_9, 3 H_{Ph}), 6.36 (d, 1H, H_6, J = 0.8 Hz), 2.56 (d, 3H, J = 1.2 Hz, CH_3)	164.5 (C_2), 160.5 (C_7), 152.5 (C_5), 152.2 (C_{8a}), 151.7 (C_{9a}), 138.9 (C_{3a}), 132.1 (C_{Ph}), 128.9 (C_{Ph}), 127.7 (C_{Ph}), 126.1 (C_{Ph}), 117.6 (C_{4a}), 114.8 (C_4), 113.8 (C_6), 99.2 (C_9), 19.1 (CH_3)

In the present work, a modified Lindemann's pyrolysis method (out of solvent) was utilized in the synthesis of benzisoxazole derivatives (**5a-c**). The chromenoisoxazole and chromenooxazole were synthesized either by pyrolysis of the corresponding O-acetyl derivative **11** or by reflux in pyridine. Thus, pyrolysis of **11** gave a 1:1 mixture of chromenoisoxazole **12** and chromenooxazole **13**, while cyclization in refluxing pyridine the ratio of **12** to **13** was higher (3:1). The overall yields were similar in both cases.

In summary, the present study provides a convenient method for the synthesis of linear furocoumarins and their transformation into chromenoisoxazols and chromenooxazols. We have also developed a simple and efficiently method to prepare 6-substituted 1,2-benzisoxazoles which could be widely applicable to the preparation of relevant pharmaceutical compounds containing a benzisoxazole ring.

EXPERIMENTAL SECTION

Melting points are uncorrected. IR spectra were recorded on Perkin-Elmer FT-IR 1720 X spectrophotometer as neat KBr disks. ^{1}H-NMR spectra were determined on a Bruker AM-400 spectrometer. The ^{13}C-NMR spectra were obtained of the same instruments operating at 100 MHz. High resolution mass spectra were determined on a VG-7070 mass spectrometer at 70 eV, and all the other mass spectra were obtained on a Ribemag 10-10 spectrometer using EI (70 eV). Elemental analyses were performed by the Analytical Division of the Chemistry Institute of Fribourg.

Preparation of 2-Hydroxy-4-halobenzophenone Oximes (3a-f).- A mixture of the 2-hydroxy-4-halobenzophenone **2a-f** (3 mmol), KOH (1 g, 1.8 mmol), hydroxylamine hydrochloride (0.5 g, 7.2 mmol) and 10 mL water was heated for 10 minutes resulting a yellow suspension. After cooling, 20 mL of water was added and the initial suspension was transformed into a clear yellow solution.

Bubbling of a stream of CO_2 into the solution afforded the desired products **3a-f** which separated as a white solid, and was purified by recrystallization from EtOH.

Preparation of O-Acetyl-2-hydroxy-4-halobenzophenone Oximes (4a-f), General Procedure.- A mixture of the 2-hydroxy-4-halobenzophenonoxime **3a-f** (3 mmol) and fresh distilled acetic anhydride (6 mL) was stirred at room temperature until a solution was obtained. After few minutes, the solid of 2-hydroxy-4-halobenzophenonoxime acetates (**4a-f**) precipitated and was purified by recrystallization from EtOH.

Preparation of 6-Halo-3-phenyl-1,2-benzisoxazoles (5a-f).- For 20 minutes, 5 mmol of a O-acetyl-2-hydroxy-4-halobenzophenonoxime **4a-f** was heated on an oil bath at 165-180° and 5 mm Hg pressure. The resulted crude product was purified by recrystallization from EtOH yielding the desired 1,2-benzisoxazoles (**5a-f**).

2,3-Diphenyl-5-methylfuro[3,2-g] [1]benzopyran-7-one (7).- A mixture of 12.0 g (68 mmol) coumarin, 14.0 g (68mmol) benzoin and 6.2 g (100mmol) of boric acid was heated in the oil-bath at 180-200°C for 2 h. The reaction mixture was poured into a beaker containing 100 mL methyl acetate. The solid was collected and recrystallized from benzene.

4-Methyl-7-benzoyloxy-6-benzoylchromen-2-one (8).- A mixture of 3.0 g (8.4 mmol) of coumarin **7** and 70 mL acetic acid was heated on the steam bath resulting in a clear solution, and then it was added to 1.7 g (17 mmol) CrO_3 and dissolved in 60 mL hot acetic acid. The reaction mixture was heated for 2 h at reflux. After cooling, 200 mL water was added to the solution and the obtained precipitate was collected. The crude compound recrystallized from ethanol.

4-Methyl-7-hydroxy-6-benzoyl-chromen-2-one (9).- A solution of 3.0 g (11mmol) of **8** in 25 mL ethanol was treated with 1.5 (37.5mmol) g NaOH in 5 mL water and the resulting orange solution was refluxed for 10 minutes. After cooling, a moderate stream of CO_2 was bubbled into the solution and a yellow solid precipitated. The crude compound recrystallized from ethanol.

7-Hydroxy-6-(Hydroxyiminobenzal)-4-methylchromen-2-one (10).- A solution of 2 mmol carbonyl compound **8** or **9** and hydroxylamine hydrochloride (some amount in weight as the latter) in a 10:1 v/v mixture of ethanol and pyridine (with the latter in the same amount in volume as **8** or **9** the carbonyl derivative) was refluxed with stirring for 22 hrs. The mixture was poured into ice-water, acidified to pH ~ 3 with conc. hydrochloric acid to afford a white solid. The product was washed with a solution 10% of hydrochloric acid to remove pyridine and recrystallized from ethanol to give 470 mg (80%) of **10** from **8** and 260 mg (40%) of **10** from **9.**

7-Hydroxy-6-(acetoxyminobenzal)-4-methylchromen-2-one (11).- A mixture of **10** (0.2 g, 0.64 mmol) and fresh distilled acetic anhydride (3 mL) was stirred at room temperature until a clear solution was obtained. After few minutes, the crude solid which precipitated was washed with water and recrystallized from ethanol.

Pyrolysis of 11.- Compound **11**, (200 mg, 0.63 mmol) was heated for 5 min. in an oil bath at 165-180° and 5 mm Hg pressure. The resulted crude product was purified by chromatography on a silica gel column with a mixture of CH_2Cl_2:AcOEt:hexane (16:4:1) as eluent to obtain 70 mg (40%) of 4-

methyl-6-phenylchromeno[6,7-d]isoxazol-7-one (**12**) and 70 mg (40%) of 4-methyl-7-phenylchromeno[6,7-d]oxazol-7-one (**13**).

Cyclisation of 11: Compound **11** (200 mg , 0.63 mmol) was refluxed with dry pyridine (3 mL), for about 3 h in an oil bath. The reaction mixture was then poured over ice containing enough hydrochloric acid (pH~3) to neutralize pyridine. The solid compound obtained was collected and separated by flash chromatography as above to obtain 98 mg (60 %) of **12** and 33 mg (20 %) of **13**.

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