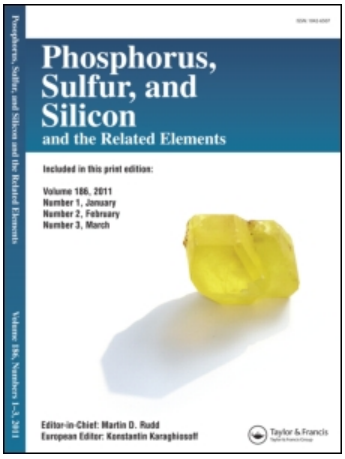

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The Behavior of Certain Coumarins and Furocoumarins Toward Sulfur Reagents

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The Behavior of Certain Coumarins and Furocoumarins Toward Sulfur Reagents

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*The behavior of 4-hydroxycoumarin (**1**), 7-hydroxycoumarin (**2**), 4-hydroxybergapten (**3**), and 4-hydroxyisopimpinellin (**4**) toward sulfur reagents, namely, thionyl chloride, phosphorus pentasulfide, thiolacetic acid, and Lawesson's reagent (**5**), was studied. The nature of products in each case depended upon the type of reactants and reaction conditions. Possible reaction mechanisms were considered, and structural elucidations of the new products were based upon compatible elementary and spectroscopic evidences.*

Keywords Coumarins; furocoumarins; sulfur reagents; thiation, chlorination

INTRODUCTION

Coumarins and furocoumarins constitute two important classes of compounds, many of which exhibit useful drug activity.[1–7] They act as hepatoprotective,[8,9] antiinflammtory and antiallergic,[10,11] antimicrobial and anti-HIV,[12,13] and antimitotic and anticancer[14–16] agents. They also act as effective photoreactive cross-linkage reagents for nucleic acids.[17] The chemistry of coumarins and furocoumarins has received considerable interest.[3,18–20] Relatively limited attention, however, was paid for studying their behavior toward sulfur reagents.[21] This together with our growing interest in this area[22–25] has prompted us to study the behavior of 4-hydroxycoumarin (**1**), 7-hydroxycoumarin (Umbelliferone, **2**), 4-hydroxybergapten (**3**), and 4-hydroxyisopimpinellin (**4**) toward a number of sulfur reagents, namely, thionyl chloride, phosphorus pentasulfide, thiolacetic acid, and 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane-2,4-disulfide(Lawesson's Reagent, LR, **5**) (Schemes 1, 2).

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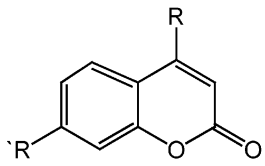
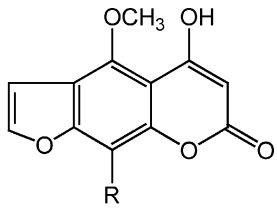
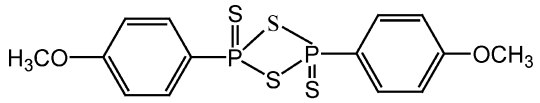




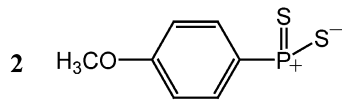
1, R = OH; R` = H
2, R = H; R` = OH

3, R = H
4, R = OCH_3

SCHEME 1



5 A



5 B

SCHEME 2

RESULTS AND DISCUSSION

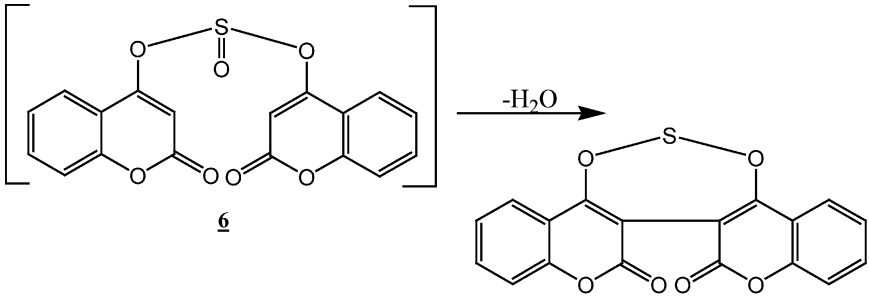
Reactions With Thionyl Chloride

Upon heating compound **1** with thionyl chloride in the absence of a solvent, a light orange crystalline substance was obtained and assigned structure **7** for the following reasons: (**a**) Correct elementary analyses and molecular weight determination (MS) corresponded to $C_{18}H_8O_6S$. (**b**) The strong OH absorption band present in the IR spectrum of **1** at 3360 cm^{-1} was absent in the spectrum of **7**. (**c**) The mass spectrum of **7** showed the molecular ion peak at m/z 352 (M^+, 55%).

Apparently, the reaction of **1** with $SOCl_2$ proceeds via initial dehydrochlorination involving the hydroxyl group in **1** to give the intermediate bis-product **6**. The tendency of **1** to form bis-compounds is noticed in its reaction with many reagents, e.g., aldehydes.[20] The intramolecular dehydration of **6** yields **7** (Scheme 3).

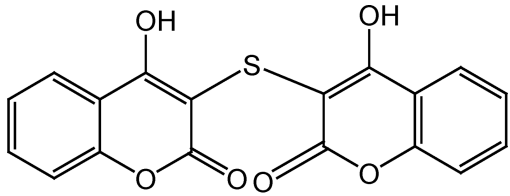
On this basis, structure **8**, formerly proposed by Klosa[21] for the same reaction product of **1** with $SOCl_2$, can be dismissed (Scheme 4).

On the other hand, when 4-hydroxybergapten (**3**) was allowed to react with $SOCl_2$ in the absence of a solvent, it yielded a colorless



6 **7**

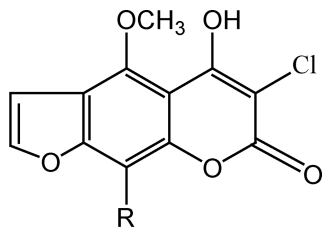
SCHEME 3



8

SCHEME 4

crystalline material formulated as 6-chloro-5-hydroxy-4-methoxy-7H-furo[3,2-g][1]benzopyran-7-one (**9**) (Scheme 5) for the following reasons: (**a**) Elementary analyses and molecular weight determination (MS) for **9** corresponded to $C_{12}H_7ClO_5$.



9, R = H
10, R = OCH_3

SCHEME 5

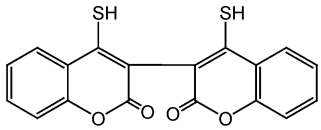
(**b**) Its IR spectrum (KBr, cm^{-1}) showed strong absorption bands at 3237 (OH), 1718 (C=O, lactone), 1637, 1576, 1551 (C=C, aromatic and furan), 1162 (C–O, stretching), and 751 (Cl–C). (**c**) The ^1H NMR spectrum of **9** (DMSO/D_2O, δ ppm) revealed the presence of two singlets at 4.34 (3H,

OCH_3) and 7.48 (1H, HC-9) and two doublets (each with $J_{HH} = 2.5$Hz) due to the furan ring protons at 8.10 and 7.40. Moreover, the HC-3 proton present in the spectrum of **3** at δ 6.5 was absent in the spectrum of **9**. The mass spectrum of **9** showed the molecular ion peak at m/z 266 (268).

In the same sense, 4-hydroxyisopimpinellin (**4**) yielded the respective 3-chloro-derivative (**10**) upon heating with $SOCl_2$ in the absence of a solvent (Scheme 6). Structure **10** was supported with compatible elementary and spectroscopic measurements (Tables I and II).

Reactions With Phosphorus Pentasulfide

When a mixture of 4-hydroxycoumarin (**1**) and $(P_2S_5)_x$ in dry toluene was boiled under reflux, it yielded an orange-red crystalline substance formulated as 3,3′-bis-(4-thiohydroxycoumarin) [4-mercapto-3-(4-mercapto-2-oxo-2H-chromen-3-yl)-2H-chromen-2-one] (**11**) for the following reasons: (**a**) The correct elementary and molecular weight determination (MS) for **11** corresponded to $C_{18}H_{10}O_4S_2$. (**b**) Its mass spectrum (m/z, %) showed ion peaks at 354 (M^+, 100%) and at 321 (M-SH radical, 95%).



11

SCHEME 6

Under similar conditions, 7-hydroxycoumarin (**2**) reacted with $(P_2S_5)_x$ to give a golden yellow crystalline product formulated as 7-hydroxy-2H-chromene-2-thione (**12**) (Scheme 7). Its elementary analyses and molecular weight determination (MS) confirmed a molecular formula of $C_9H_6O_2S$. The mass spectrum of **12** showed the molecular ion peak at m/z 178 (100%). A loss of 44 mass units (CS) from M^+ yielded the peak at m/z 134 (92.1%). The IR spectrum of **12** revealed the presence of hydroxyl group absorption around 3250 cm^{-1} and the absence of the lactone carbonyl band around 1700 cm^{-1}.

The ^{1}H NMR spectrum of **12** (DMSO, δ ppm) disclosed 3 sets of doublets (each with $J_{HH} = 15$ Hz) at 7.75 (HC-3), 7.60 (HC-4), and 7.00 (HC-5), as well as a multiplet centered at 6.85 (2H) due to (HC-6) and its *m*-coupling with (HC-8). The ^{1}H NMR spectrum also disclosed a singlet at 11.00 due to OH group (D_2O exchangeable). On this basis, the other alternative structure **13** can be overlooked (Scheme 8).

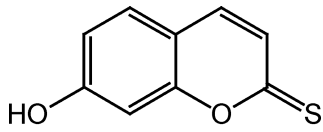
TABLE I Physical, Analytical, and IR Spectral Data of Compounds 7, 9, 10, 11, 12, 14, 17, 19, and 20

					Analysis Calcd./Found					IR (cm^{-1})						
Compound	Yield %	M.P. (°C)	Mol. Formula (Mol. Wt.)	M^+ m/z(%)	C%	H%	Cl%	P%	S%	OH	SH	C=O	C=C Aromatic	C=S	C—O Stretch.	Cl—C
7	70	300	$C_{18}H_8O_6S$ (352.31)	352 (55)	61.36 60.92	2.29 2.31	—	—	9.10 8.80	—	—	1804 (lactone)	1635–1568	—	1317	—
9	60	300	$C_{12}H_7ClO_5$ (266.64)	266 (75) 268	54.06 54.42	2.65 2.20	13.30 12.82	—	—	3237	—	1718 (lactone)	1637–1551	—	1162	751
10	65	270	$C_{13}H_9ClO_6$ (296.62)	296 (100) 298	52.63 52.40	3.06 2.80	11.95 11.60	—	—	3263	—	1712 (lactone)	1635–1597	—	1144	754
11	65	161–163	$C_{18}H_{10}O_4S_2$ (354.39)	354 (100)	61.00 61.34	2.84 2.80	—	—	18.10 17.63	—	2430	1807 (lactone)	1690–1525	—	1137	—
12	60	258–260	$C_9H_6O_2S$ (178.21)	178 (100)	60.66 60.28	3.39 3.10	—	—	17.99 17.65	3250	—	—	1627–1519	1178	1240	—
14	50	110	$C_{12}H_8O_3S_2$ (264.33)	264 (100)	54.53 54.21	3.05 3.22	—	—	12.13 11.87	—	2488	—	1627–1500	1154	1281	—
17	50	205	$C_{12}H_7O_3PS_5$ (390.49)	390 (25)	36.91 37.22	1.81 1.74	—	7.93 7.50	41.06 40.76	—	2472	—	1624–1536	1125	1220	—
18	75	217	$C_9H_6OS_2$ (194.28)	194 (100)	55.64 55.22	3.11 2.85	—	—	33.01 33.35	—	2373	—	1600–1530	1137	1256	—
19	55	113–114	$C_{13}H_{10}O_4S_2$ (294.35)	294 (100)	53.05 53.15	3.42 3.15	—	—	21.79 21.39	—	2476	—	1600–1510	1237	1300	—
20	75	140	$C_{11}H_8O_4$ (204.18)	204 (25)	64.71 64.27	3.95 3.66	—	—	—	—	—	1780 (lactone) 1743 (ester)	1620–1565	—	1204	—

TABLE II ^{1}H NMR Spectral Data for Compounds 7, 9, 10, 11, 12, 14, 17, 18, 19, and 20

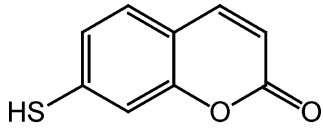
Compound	^{1}H NMR (DMSO-d_6 or $CDCl_3$, δ ppm) Values
7[a]	7–8.05(*m*, 8H, aromatics)
9[a]	4.34(*s*, 3H, OCH_3); 7.4, 8.1(2*d*, each with $J_{HH} = 2.5$Hz, 2H, furan); 7.48(*s*,1H, aromatic); 11(*bs*, 1H, OH*)
10[a]	4.05, 4.20(2*s*, 6H, 2 OCH_3); 7.40, 8.15(2*d*, each with $J_{HH} = 2.5$Hz, 2H, furan); 11.15(*bs*, 1H, OH*)
11[a]	7.37–7.95(*m*, 10H, 8 aromatics & 2 SH*)
12[a]	6.85(*m*, 2H, HC-6 & HC-8); 7.00, 7.60, 7.75(3*d*, each with $J_{HH} = 15$Hz, 3H, HC-5 & HC-4 & HC-3); 11(*bs*, 1H, OH*)
14[a]	4.22(*s*, 3H,OCH_3); 4.48(*bs*, 1H, SH*); 7.40(*m*, 2H, furan & pyran); 7.62(*s*, 1H, aromatic); 8.15(*d*, $J_{HH} = 2.5$Hz, 1H, furan)
17[b]	4.00(*s*,1H, SH*); 4.25(*s*, 3H, OCH_3); 7.171–7.179(*d*, 1H, $J_{HH} = 2.1$Hz, furan); 7.80(*s*, 1H, vinyl proton); 7.82–7.81(*d*, $J_{HH} = 2.1$Hz, 1H, furan)
18[a]	7.05(*s*, 1H, HC-3); 7.15–7.85(*m*, 5H, aromatics & SH*)
19[a]	3.96(*bs*, 1H, SH*); 4.11, 4.22(2*s*, 6H, 2 OCH_3); 6.96, 6.97(*d*, $J_{HH} = 2.5$Hz, 1H, furan); 7.12(*s*, 1H, vinyl proton); 7.67, 7.68(*d*, $J_{HH} = 2.5$Hz, 1H, furan).
20[a]	3.25(*s*, 3H, CH_3COO); 6.50(*d*, $J_{HH} = 9.3$Hz, HC-3); 7.18(*d*, $J_{HH} = 10.5$Hz, HC-6); 7.30(*d*, $J_{HH} = 2.4$Hz, HC-8); 7.80(*d*, $J_{HH} = 8.4$Hz, HC-4); 8.50(*d*, $J_{HH} = 9.9$Hz, HC-5).

[a]DMSO-d_6.
[b]$CDCl_3$.
*Exchangeable with D_2O.



12

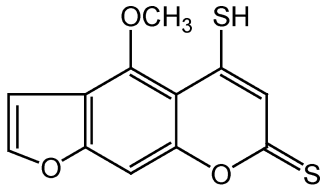
SCHEME 7



13

SCHEME 8

4-hydroxybergapten (**3**) reacted with $(P_2S_5)_x$ in boiling toluene to give a yellow product formulated as 5-mercapto-4-methoxy-7H-furo[3,2-g][1]benzopyran-7-thione (**14**) (Scheme 9) for the following reasons: (**a**) Correct elementary analyses and molecular weight determination (MS)



14

SCHEME 9

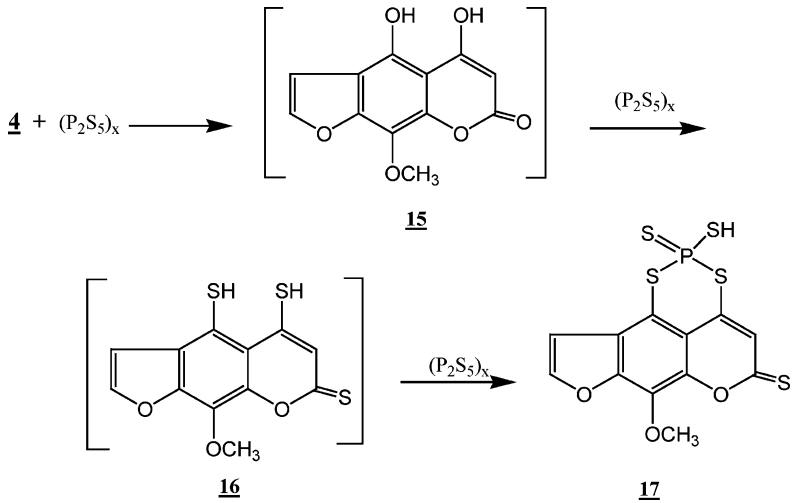
corresponded to $C_{12}H_8O_3S_2$. (**b**) Its IR spectrum (KBr, cm^{-1}) disclosed the absence of carbonyl absorption in the 1750–1650 region.

On the other hand, the spectrum showed a medium band at 2472 (SH) and a strong band at 1154 (C=S).[26] Strong bands were also present in the 1627–1500 region (C=C, furan and aromatic). (**c**) The ^1H NMR of **14** (DMSO, δ ppm) showed signals at 4.22 (*s*, 3H, OCH_3), 8.15 (*d*, $J_{HH} = 2.5$ Hz, lH, furan), 7.62 (*s*, lH, aromatic), and 7.40 (*m*, 2H, furan and pyran). The SH proton appeared as a broad singlet at 4.48 ppm. The reaction of 4-hydroxyisopimpinellin (**4**) with $(P_2S_5)_x$ proceeded in boiling toluene to give a yellow crystalline substance for which structure **17** is assigned. Structural reasonings for **17** are as follows; (**a**) Elementary analyses and molecular weight determination (MS) agreed with the molecular formula, $C_{12}H_7O_3PS_5$. (**b**) The IR spectrum of **17** (KBr, cm^{-1}) revealed the absence of carbonyl group absorption in the 1750–1650 cm^{-1} region. (**c**) The ^1H NMR spectrum of **17** (DMSO or $CDCl_3$ δ ppm) showed one singlet due to the OCH_3 protons at 4.25. Signals were also found at 7.80 (*s*, 1H, HC-3), 7.82–7.81 (*d*, $J_{HH} = 2.1$ Hz, 1H, HC-6, furan), 7.179–7.171 (*d*, $J_{HH} = 2.1$ Hz, 1H, HC-7, furan), and 4.00 (SH, D_2O-exchangeable).

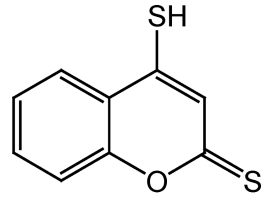
A mechanism for the formation of **17** is depicted in Scheme 10. It involves the initial partial demethylation of **4** under the influence of the thiating agent[27] to give **15**. Intermediate **15** then undergoes thiation with the same reagent to afford **16**, which reacts with an additional molecule of $(P_2S_5)_x$ to afford the final product **17**.

Reactions With Lawesson's Reagents (LR, 5)

4-hydroxycoumarin (**1**) reacted with LR **5** in boiling toluene to give a golden yellow crystalline product formulated as 4-thiohydr-oxycoumarin-2-thione (4-mercapto-2H-chromene-2-thione) (**18**) (Scheme 11) for the following reasons: (**a**) Elementary analyses and molecular weight determination (MS) for **18** corresponded to $C_9H_6OS_2$. (**b**) Its IR spectrum (KBr, cm^{-1}) revealed the absence of OH absorption around



SCHEME 10



18

SCHEME 11

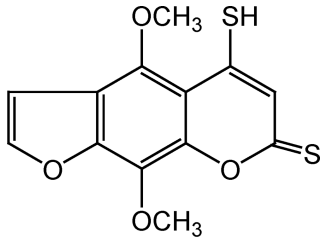
3400 and the absence of the lactone-carbonyl around 1750, while the SH absorption band appeared at 2373.

(**c**) Its ^{1}H NMR spectrum (DMSO, δ ppm) showed the HC-3 proton as a singlet at 7.05 and the aromatic protons (4H) as a multiplet in the region 7.85–7.15 ppm. The mass spectrum of **18** showed the molecular ion peak at m/z 194 (100%). Prominent ion peaks were also observed in the spectrum at m/z 161 (M-SH radical, 16.2%) and m/z 150 (M—C═S, 47.9%).

The reaction of 7-hydroxycoumarin (**2**) with LR, **5** also proceeded in boiling toluene to give a golden yellow crystalline product proved to be 7-hydroxy-2H-chromene-2-thion (**12**) based upon compatible elementary and spectoscopic analyses (comparative IR, ^{1}H NMR, and mass spectra).

LR, **5** induced thiation of both the hydroxyl group and the lactone-carbonyl group in 4-hydroxybergapten (**3**) upon refluxing together in toluene to give a yellow product formulated as 5-mercapto-7H-furo[3,2-g][1]benzopyran-7-thione (**14**) (comparative IR, ^{1}H NMR, and mass spectra).

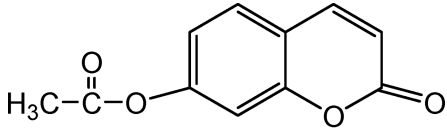
In the same sense, the thiation of 4-hydroxyisopimpinellin (**4**) with LR, **5** yielded a compound formulated as 4,9-dimethoxy-5-mercapto-7H-furo[3,2-g][1]benzopyran-7-thione (**19**) almost exclusively (Scheme 12).



19

SCHEME 12

The reaction of 7-hydroxycoumarin with thiolacetic acid proceeded in boiling toluene to give a white crystalline material formulated as 7-acetoxycoumarin (**20**) (Scheme 13) for the following reasons: (**a**) Correct elementary and molecular weight determination (MS) corresponded to $C_{11}H_8O_4$. (**b**) Its IR spectrum (KBr, cm^{-1}) revealed the absence of OH group absorption around 3400, while strong bands were recorded in the spectrum at 1780 (C═O, lactone), 1620, 1565 (C═C, aromatic), and 1204 (C—O, stretching).



20

SCHEME 13

(**c**) Its ^{1}H NMR spectrum (DMSO, δ ppm) showed 5 sets of doublets at 8.50 (HC-5, $J_{HH} = 9.9$ Hz), 7.80 (HC-4, $J_{HH} = 8.4$ Hz), 7.30 (HC-8, $J_{HH} = 2.4$ Hz due to *m*-coupling with HC-6), 7.18 (HC-6, $J_{HH} = 10.5$ Hz), and 6.50 (HC-3, $J_{HH} = 9.3$ Hz). Protons of the CH_3COO group appeared as a singlet (3H) at $\delta = 3.25$ ppm. (**d**) The mass spectrum of **20** showed prominent ion peaks at m/z 204 (M^+, 25.5%), m/z 162 (M—$COCH_2$, ion

a, 99.7%), and m/z 134 (ion **a**-CO, 100%). Moreover, compound **20** was also unequivocally prepared and identified (comparative IR, ^{1}H NMR, and mass spectra) by the acetylation of 7-hydroxycoumarin (**2**) with boiling acetic anhydride.[28]

EXPERIMENTAL

All melting points were determined on an electro-thermal melting point apparatus and were uncorrected. The infrared spectra were carried out in KBr on a Philips Infracord. Microanalyses were carried out at the Micro-Analytical laboratory at the National Research Centre, Dokki, Cairo, Egypt. ^{1}H NMR spectra were measured with a Jeol-GLM 270 MHz (superconducting magnet) in DMSO or $CDCl_3$, and chemical shifts were recorded in δ-scale ppm relative to TMS as an internal standard. Mass spectra were run at 70 eV with a Finnigan SSQ GC/MS spectrometer using the electron Ionization Technique.

The Reaction of 4-Hydroxycoumarin (I), 4-Hydroxybergapten (3), and 4-Hydroxyisopimpinellin (4) With Thionyl Chloride

General procedure

A solution of the coumarin derivative (0.005 mol) in 10 mL of thionyl chloride was refluxed in the absence of a solvent on a steam bath for 10–15 h. After the evaporation of the volatile materials in vacuo, the remaining solid material was collected and recrystallized from the appropriate solvent to give compounds **7**, **9**, and **10**. Physical, analytical, and spectral data of compounds **7**, **9**, and **10** are presented in Tables I and II.

The Reaction of Compounds 1, 2, 3, and 4 with Phosphorous Pentasulfide

General procedure

The coumarin derivative (0.005 mol) and 1 g $(P_2S_5)_x$ purified by cautious extraction with CS_2 (Soxhlet) were mixed in 20 mL of toluene and refluxed for 8 10 h (TLC). The reaction mixture was filtered while hot, and the volatile materials were evaporated from the filtrate *in vacuo* on a small amount of silica gel until dryness. Then the mixture was separated by column chromatography using acetone/pet. ether (b.p. 60–80°C) as the eluent to give compounds **11**, **12**, **14**, and **17**. Physical, analytical, and spectral data of compounds **11**, **12**, **14**, and **17** are presented in Tables I and II.

The Reaction of Compounds 1, 2, 3, and 4 with Lawesson's Reagent (LR, 5)

General procedure

A mixture of the coumarin derivative (0.005 mol) and 0.005 mol of Lawesson's reagent in 20 mL of acetonitrile (or toluene) was refluxed for 8–10 h (the reaction was controlled with TLC). The volatile materials were then evaporated *in vacuo* on a small amount of silica gel until dryness, and the mixture was separated with column chromatography using acetone/pet. ether (b.p. 60–80°C) as the eluent. Compounds **18**, **12**, **14**, and **19** were separated and purified.

Their physical, analytical, and spectral data are presented in Tables I and II.

The Reaction of 7-Hydroxycoumarin (2) With Thiolacetic Acid

A mixture of 7-hydroxycoumarin (0.81 g, 0.005 mol) and 1 mL of thiolacetic acid in 20 mL of toluene was refluxed for 6 h. After evaporating the volatile materials in vacuo, the remaining solid was collected and recrystallized from acetone to give **20** as a white powder, m.p. and mixed m.p. 140°C.[28]

The Acetylation of 2

7-hydroxycoumarin (**2**) (0.81 g, 0.005 mol) was refluxed with acetic anhydride for ca 5 h; then the reaction mixture was cooled, poured onto ice, and left overnight. The formed precipitate was filtered, dried, and recrystallized from acetone to give **20** (m.p.; mixed m.p; and comparative IR, ^{1}H NMR, and mass spectra).

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