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Reactions of Flavonoid Thiosemicarbazones under Acetylating Conditions

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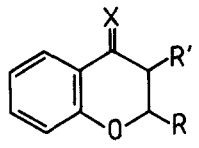
Abstract: Upon acetylation, (2-phenyl)dihydrobenzopyrone- and 2'-hydroxychalcone thiosemicarbazones (1c, 2c, 3c, and 7c) form 2,2-disubstituted 5-acetamido-3-acetyl-2,3-dihydro-1,3,4-thiadiazoles (1i, 2i, 4i, and 8i) instead of the diacetylthiosemicarbazones (2e, 8e) claimed in the literature Similarly, the reactions of the aromatic ketone thiosemicarbazones 9c, 10c and 11d result in the formation of thiadiazolines (9i, 10i, and 11k, respectively), flavone thiosemicarbazone (6c), however, is degraded to flavone diacetylhydrazone (6g) under the same conditions The synthesis of the flavanone spiro-1,3,4--oxadiazoline 2h is also described

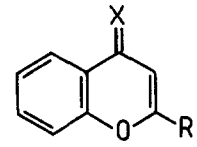
INTRODUCTION

It is known that acetylation of aliphatic or aromatic aldehyde thiosemicarbazones affords 2-substituted 5-acetamido-3-acetyl-2,3--dihydro-1,3,4-thiadiazoles[1-5] (and the application of chiral synthons allows the synthesis also of the C-2 epimers with high optical rotation values[5,6]). The thiosemicarbazones of aliphatic and alkyl-aryl ketones undergo an analogous reaction[2,7].

The presence of an sp^2 hybridized carbon neighbouring the carbonyl group lowers the rate of formation of the thiosemicarbazones, and may also influence the direction of the transformation of the latter under acylating conditions. The present paper deals with the synthesis of the thiosemicarbazones of diversely substituted flavonoid compounds bearing carbon atoms of various oxidation state, and also with the examination of their transformation under acylating conditions.



	R	R′
1	H	H
2	Ph	H
3	Ph	OH
4	Ph	OAc



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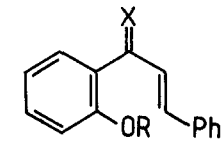
6 R = Ph



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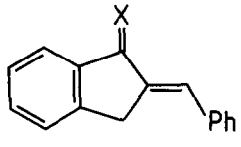
8 R = Ac



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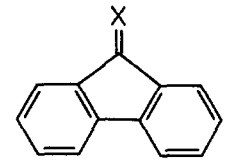

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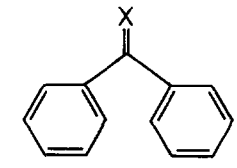
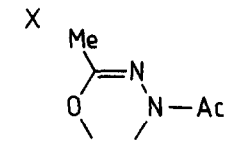


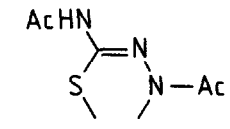
11

	X
a	O
b	N NH_2
c	N·NH CS NH_2
d	N NH CS NHPh
e	N NH CS NAc_2
f	N NHAc
g	N NAc_2

h



i



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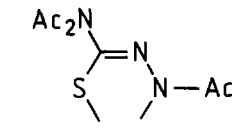

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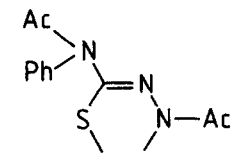

RESULTS AND DISCUSSION

The reaction of 4-chromanone thiosemicarbazone (**1c**) with acetic anhydride in pyridine gave spiro[5-acetamido-3-acetyl-2,3-dihydro--1,3,4-thiadiazole-2,4′-chroman] (**1i**) as the major product, accompanied by minor quantities of the corresponding 5-diacetylamino derivative **1j**. The spiro-structure of these compounds was clearly proved by the S-CRR′-NAc signal in the ^{13}C-NMR spectrum of **1i** at δ = 75.64 ppm, and by the indentical mass spectrometric fragmentation pattern of both compounds (**1i** and **1j**) with *m/e* 179 and 178, respectively, characteristic of spiro-thiazirine fragments[3,7]. For comparative studies 4-chromone (**5a**) was not suitable, since under the conditions of the thiosemicarbazone--formation reaction it was reported[8] to be transformed, with ring cleavage, into 3-(2-hydroxyphenyl)-1-thiocarbamoyl-5-thiosemicarbazido--2-pyrazoline in an atypical reaction favoured by the known tendency for chromylium salt-formation.

Treatment of the flavanone thiosemicarbazone **2c**, and of the structurally isomeric 2′-hydroxychalcone thiosemicarbazone (**7c**) with acetic anhydride in pyridine gave 2,2-disubstituted-1,3,4-thiadiazoline derivatives (**2i** and **8i**). The spiro[5-acetamido-3-acetyl-2,3-dihydro--1,3,4-thiadiazole-2,4′-flavan] structure of **2i** was assigned by comparison with the above mass- and ^{13}C-NMR spectral criteria of the chroman analogue **1i** [*m/e* 255 (thiazirine + 1), δ = 76.99 (spiro carbon); see Tables 1 and 2]. The considerably different chemical shift ($\Delta\delta$ = 0.88 ppm) of the H-3 and H-3′ protons of the flavan ring in **1i** may be attributed to the selective steric shielding effect of the endocyclic acetamido group. The thiadiazoline structure **8i** of the product obtained upon acetylation of **7c** was proved by the data: *m/e* 280 (*N*-acetylthiaziridine derivative - OAc) and the δ = 79.36 ppm (S-*C*RR′-NAc) chemical shift value in the ^{13}C-NMR spectrum. Thus, the earlier reports[9] in the literature, claiming the formation of diacetyl-thiosemicarbazones **2e** and **8e** upon acetylation of the thiosemicarbazones **2c** and **7c**, must be considered erroneous.

Although thioacylhydrazones possess greater tendency for ring-closure[5,17], as compared to the corresponding oxygen analogues, because of the higher nucleophilic character of the sulphur atom, we expected that the acylhydrazones of flavonoids would transform into spiro-oxadiazoline derivatives (e.g. **2h**) under acylating conditions (in hot acetic anhydride, or more conveniently[10,11], with $Ac_2O/ZnCl_2$ near room temperature). Treatment of flavanone acetylhydrazone (**2f**) or the diacetylhydrazone **2g** with $Ac_2O/ZnCl_2$ resulted, indeed, in spiro[3-acetyl-5-methyl-2,3-dihydro--1,3,4-oxadiazole-2,4′-flavan] (**2h**). The spiro-oxadiazoline structure of

2h was unequivocally proved by the ^{13}C-NMR data (see Table 2), including the δ = 95.95 ppm (spiro-carbon) chemical shift. Moreover, differentiation[12,13] from the isomeric diacetylhydrazone structure could be made according to the δ = 11.51 ppm [O-C(CH_3)=N-] signal appearing at significantly higher field than the acetyl-methyl signal of the isomeric diacetylhydrazone (δ = 22.33 ppm). In accordance with the spiro-3-acetyl-oxadiazoline structure **2h** a significant difference (1.16 ppm) between the ^{1}H-NMR chemical shift values of the H-3 and H-3′ protons was observed similarly to the thiadiazoline derivative **2i** (see above). Based on the elemental analysis data and m.p. the product proved to be identical with the material previously prepared[14] by the acetylation of flavanone hydrazone (**2b**) with acetic anhydride "under more drastic conditions (140°C)" and mistakenly claimed to be "the diacetyl derivative of the flavanone hydrazone" (**2g**).

Acetylation of *trans*-3-hydroxyflavanone thiosemicarbazone (*trans*-**3c**), containing asymmetric carbon neighbouring the prochiral reaction centre, gave two optically inactive products with identical elemental composition. Based on the ^{13}C-NMR spectral data [δ = 78.98 and 81.36 ppm, respectively, (spiro-carbon)] both products have the spiro[5-acetamido-3-acetyl-2,3--dihydro-1,3,4-thiadiazole-2,4′-*trans*-3′-acetoxyflavan] structure (**4i** I and **4i** II), differing from each other only in the configuration of the spirocarbon. This was clearly supported by the ^{1}H-NMR spectra (see Table 2), showing different chemical shift for one of the three acetyl groups and for the H-2 and H-3 protons of the flavan rings.

Flavone thiosemicarbazone (**6c**) reacted in a way completely different from the previously discussed transformations of the dihydrobenzopyran--type (**1-3**) or chalcone (**7a**) thiosemicarbazones. Thus, treatment of **6c** with acetic anhydride in pyridine afforded a product which did not contain sulphur, *i e* flavone diacetylhydrazone (**6g**). This was rather surprising since, to our knowledge, the known degradation[5,15-17] of semicarbazones into (di)acetylhydrazones has not been observed with thiosemicarbazones. On the bases of spectral data [ν_{max}(KBr) 1707 and 1686 cm^{-1} (NAc_2); δ = 2.50 ppm (s, 6H, 2C*H*$_3$-CO), and the single peak for the two CH_3-CO at δ = 25.82 ppm, as well as, *m/e* = 321 (M^+ + 1); see Table 1 and 2], elemental analyses, m.p. and tlc R_F data, the product (**6g**) was found to be identical with an authentic sample[18] of flavone diacetylhydrazone. Since under the given acetylating conditions each of the 2-benzylideneindanone and 9-fluorenone thiosemicarbazones, as well as benzophenone 4-phenyl-thiosemicarbazone (**9c**, **10c** and **11d**, respectively), carrying a similar sp^2 carbon in the neighbourhood of the hydrazone function, transform into the corresponding 2,3-dihydro-1,3,4-thiadiazole derivative (**9i**, **10i** and **11k**),

Table 1. Preparation and Physical Data of **1i, 1j, 2h, 2i, 4i, 6g, 8i, 9i, 10i, 11k**

Compound	Starting material	Acylation agent (mol)[a]	Reaction time (temp.)	Processing[b]	Yield, % crude (pure)[c]	m.p.[d] (solvent)	Formula (m.w.)	Analysis found (calcd.) C	H	N	S	MS[e] *m/e*
1i	**1c**	Ac_2O/Py (23; 5.5)	5 hr (100°)	CEI	92 (65)[f]	230° (EtOH)	$C_{14}H_{15}N_3O_3S$ (305.35)	55.37 (55.06)	5.10 (4.95)	13.77 (13.76)	10.72 (10.50)	306(M^++1) 179,178
1j	**1c**	Ac_2O/Py (23; 5.5)	5 hr (100°)	(CE)[g]I	10 (8.8)[h]	129-130° (EtOH-heptane)	$C_{16}H_{17}N_3O_4S$ (347.39)	55.76 (55.32)	5.19 (4.93)	11.81 (12.10)	9.46 (9.23)	348(M^++1) 305(M-Ac) 179,178
2h	**2f**[9,20]	$Ac_2O/ZnCl_2$ (30, 2)	23 hr (r.t.)	CFI	93 (75)[l]	178-179° (EtOH-heptane)[j]	$C_{19}H_{18}N_2O_3$ (322.35)					
	2g[20]	$Ac_2O/ZnCl_2$ (33; 2 3)	40 hr (r.t)	AI	97 (67)[l]	179-180° (EtOH-heptane)[j]	$C_{19}H_{18}N_2O_3$ (322.35)	70.14 (70.79)	5.80 (5.63)	8.92 (8.69)		
2i	**2c**[9]	Ac_2O/Py (16; 18)	5 hr (100°)	CFGI[k]	100 (63)[l]	166-168° (EtOAc-hexane)[k,m]	$C_{20}H_{19}N_3O_3S$ (381.44)			10.85 (11.02)	8.62 (8 41)	381(M^+) 255 (thiazirine+1)
4i	**3c**	Ac_2O/Py (34, 20)	5 hr (100°)	CFGH[n]I	*i* 100 (56)[o]	229° (EtOAc)	$C_{22}H_{21}N_3O_5S$ (439 48)	59 82 (60 12)	4.93 (4 82)	9.25 (9.56)	7.44 (7 30)	
					ii (5)[p,q]	168° (EtOAc)		60 23 (60 12)	4 94 (4.82)	9 23 (9.56)	7 37 (7 30)	

to be continued

Table 1 continued

	6c[18,19]	Ac_2O/Py	5 hr	BI	82	224-225° [s]	$C_{19}H_{16}N_2O_3$		8.24	Ø	321(M^++1)
		(16, 19)	(100°)		(51)[r]	(EtOAc)	(320.34)		(8.75)	(Ø)	278(M-CH_2CO)
6g											
	6g[18]	$Ac_2O/ZnCl_2$	20 hr	CFI	100[r,t]	223-224° [s]					
		(50; 3.5)	(44-45°)		(68)[u]	(EtOAc)					
8i	7c[9]	Ac_2O/Py	3 hr	CDI	92	145-147° [w]	$C_{22}H_{21}N_3O_4S$				423(M^+)[x]
		(60, 50)	(100°)		(80)[v]	(EtOH-heptane)	(423.47)				280
9i	9c	Ac_2O/Py	4.5 hr	CFGIH[y]I	100	164-165°	$C_{21}H_{19}N_3O_2S$	65.61	5.06	11.00	8.66	377(M^+)
		(16; 18)	(100°)		(87)[z]	(EtOAc-hexane)	(377.45)	(66.82)	(5.07)	(11.13)	(8.50)	217
10i	10c	Ac_2O/Py	5 hr	CEI	99.7	259-260°	$C_{18}H_{15}N_3O_2S$	64.02	4.49	12.43	9.32	
		(13; 15)	(100°)		(78)[α]	($CHCl_3$-EtOAc)	(337.39)	(64.07)	(4 48)	(12.46)	(9.50)	
11k	11d	Ac_2O/Py	5 hr	CFGI	99	164°	$C_{24}H_{21}N_3O_2S$	69.85	5.64	10.03	7.81	415(M^+)
		(20; 20)	(100°)		(87)[β]	(EtOAc-hexane)	(415.50)	(69.37)	(5.10)	(10.11)	(7.72)	135(PhNHAc)
												121(PhC^+S)

[a]Moles pro mole starting material. [b]See General methods of preparation (Experimental). [c]Tlc was performed on Alurolle-Kieselgel $60F_{254}$ (*Merck*) [d]Melting points are uncorrected and were determined on a Kofler block. [e]Mass spectra (70 eV) were obtained by using a VG-7035 GC/MS/DS instrument (ion current, 0.1 mA, direct insertion technique). [f]R_F (9 1 $CHCl_3$-Me_2CO) 0.24. [g]From the mother liquor of crude **11i** obtained after steps CE [h]R_F (9 1 $CHCl_3$-Me_2CO) 0 70. [i]R_F (2 1 PhH-EtOAc) 0 63 [j]Lit.[14] m.p. (for the "diacetyl derivative of flavanone hydrazone") 179-180 °C [k]Previously crystallised from ether R_F (9 1 $CHCl_3$-Me_2CO) 0 52 [m]Lit [9] m p. (for compound **2e** claimed) 196-198 °C.

to be continued

Legends to the Table 1 continued

[n]Using a 9.1 $CHCl_3$-Et_2O mixture as the eluent [o]Eluted first, R_f (9·1 $CHCl_3$-Me_2CO) 0.28. [p]Eluted second, R_f 0 16 [q]An unseparated mixture of the two isomers (*I* and *II*) was recovered in 35 % yield [r]R_f (1·1 PhH-EtOAc) 0 73. [s]Lit.[18] m p. 218-221 °C (from 95 % EtOH). [t]R_f (9 1 $CHCl_3$-Me_2CO) 0 74, homogeneous, and identical with the starting material **6g** also when using another solvent system[r]. [u]Without working up the mother liquor [v]R_f (1.1 PhH-EtOAc) 0 42. [w]Lit.[9] m.p. (for compound **8e** claimed) 148-152 °C (from EtOH). [x]30 eV [y]Using $CHCl_3$ as the eluent. [z]R_f ($CHCl_3$) 0 13, R_f (9.1 $CHCl_3$-Me_2CO) 0 41 [α]R_f (9 1 $CHCl_3$-Me_2CO) 0 35. [β]R_f ($CHCl_3$) 0.51.

Table 2. IR and Spectroscopic Charachteristics

Compound	ν_{max}^{KBr} cm^{-1}	^1H (200 MHz) δ ppm	^{13}C (50.3 MHz) δ ppm[a]
1i	3240, 3180, 3090 (NH) 1710*, 1704, 1678 (amide) 1648 (C=N) 1628-1618 (Ar) 1590, 1490 (Ar)	[b] 11.70 (s, 1H[c], NHAc) 7.29-6.73 (m, 4H, H-Ar) 4.50-4.45 (m), 4.10 (tr, *J* 12.5 Hz), 3.25-3.17 (q), 2.30 (d, *J* 12.5 Hz) (each 1H, CH_2CH_2); 2.15, 2.05 (each s, 3H, Ac)	[b] 169.45, 167.24 (*C*=O) 153.05 (S-*C*(NHAc)=N-) 75.64 (spiro C) 64.36 (C-2[d]) 34.38 (C-3[d]) 23.79, 22.44 (CH_3-CO)
1j	1745, 1713, 1697 (NAc_2) 1614, 1605, 1590, 1494 (Ar)	[e] 7.50-6.80 (4m, 4H, H-Ar) 4.56-4.47, 4.23-4.10, 3.60-3.45, 2.64-2.55 (4m, each 1H, CH_2CH_2) 2.53 (s, 6H, 2Ac), 2 28 (s, 3H, Ac)	
2h	1660 (amide) 1630* (C=N) 1603, 1578 (Ar)	[e] 5.34 (dd, 1H, $J_{2,3}$ 2 Hz, $J_{2,3'}$ 13 Hz, H-2[d]) 3.44 (q, 1H, $J_{2,3'}$, 13 Hz, $J_{3,3'}$, 14 Hz, H-3[d]) 2.28 (q, 1H, $J_{2,3}$ 2 Hz, $J_{3,3'}$, 14 Hz, H-3[d]) 2.29 (s, 3H, NAc)	[e] 166.00 (C=O) 155.33 (O-*C*Me=N-) 95.95 (spiro C) 75 92 (C-2[d])

to be continued

Table 2 continued

		2.12 (s, 3H, O-C(CH_3)=N-)	38.16 (C-3[d]) 22.33 (CH_3-CO) 11.51 (O-C(CH_3)=N-)
2i	3410 3225 (NH) 1690[*], 1670 (amide) 1639 (C=N) 1614, 1582 (Ar) 1481 (amide II or Ar)	[e] 11.03 (s, 1H[c], NHAc) 5.17 (d, 1H, $J_{2,3}$ 12 Hz, O-CHR-Ph) 3.41 (tr, 1H, J 13 Hz, CH_2) 2.53 (d, 1H, J 13 Hz, CH_2) 2.34, 1.75 (each s, 3H, Ac)	[e] 170.23, 168.99 (C=O) 153.83 (S-C(NHAc)=N-) 76.99 (spiro C) 76.34 (O-CHR-Ph) 42.38 (CH_2) 23.79, 22.27 (CH_3-CO)
4i *I*	3250 (NH) 1757 (OAc) 1700[*], 1690[*], 1668 (amide) 1645 (C=N) 1618, 1579 (Ar) 1480 (amide II)	[e] 8.48 (s, 1H[c], NHAc) 5.65 (ABq, 2H, J 11 Hz, O-CHPh-CHOAc-) 2.26, 2.09, 1.80 (each s, 3H, Ac)	[e] 170.20, 168.96, 168.15 (C=O) 155.21 (S-C(NHAc)=N-) 79.37, 78.29 (C-2[d] and C-3[d]) 78.98 (spiro C) 24.09, 22.79, 20.24 (CH_3-CO)
II	3235 (NH) 1762 (OAc) 1700[*], 1683 (amide) 1650 (C=N) 1624, 1590 (Ar) 1488 1457	[e] 10.30 (s, 1H[c], NHAc) 6.38 (d, 1H, J 10 Hz, CH-OAc) 5.00 (d, 1H, J 10 Hz, O-CHR-Ph) 2.20, 1.85, 1.71 (each s, 3H, Ac)	[e] 170.27, 169.97, 169.06 (C=O) 152.82 (S-C(NHAc)=N-) 81.36 (spiro C) 78.03 (C-2[d]) 69.48 (C-3[d]) 23.48, 22.26, 20.16 (CH_3-CO)
6g	1707, 1686 (NAc_2) 1628 (C=N and Ar) 1583, 1570 (Ar) 1551	[e] 6.43 (s, 1H, H-3) 2.50 (s, 6H, 2 Ac)	[e] 170.46 (2 C=O) 95.61 (C-3) 25.82 (2 CH_3-CO)

to be continued

Table 2. continued

8i	3215, 3140 (NH) 1769 (OAc) 1693 (amide) 1642 (C=N) 1613, 1575* (Ar)	[b] 11.78 (s, 1H[c], NHAc) 6.98 (s, 2H, Ph-CH=CH-) 2.25, 2.06, 2.05 (each s, 3H, Ac)	[b] 169.52, 168.50, 167.23 (C=O) 143.16 (S-C(NHAc)=N-) 79.36 (S-CRR'-NAc) 23.24, 22.33, 20.77 (CH_3-CO)
9i	3215, 3155 (NH) 1695, 1672 (amide) 1640 (C=N) 1613 (Ar)	[e] 9.88 (s, 1H[c], NHAc) 7.48-7.28 (m, 9H, H-Ar) 7.00 (tr, 1H, J 1 Hz, =CH-Ph) 4.28-3.88 (ABq, 2H, $J_{A,B}$ 20 Hz, CH_2) 2.30, 1.90 (each s, 3H, Ac)	[e] 169.36, 168.33 (C=O) 144.59 (S-C(NHAc)=N-) 87.28 (spiro C) 36.59 (CH_2) 23.51, 22.67 (CH_3-CO)
10i	3200, 3156 (NH) 1684, 1640 (amide)	[b] 11.98 (s, 1H[c], NHAc) 2.15, 2.13 (each s, 3H, Ac)	[b] 169.59, 166.29 (C=O) 142.81 (S-C(NHAc)=N-) 80.56 (spiro C) 23.15, 22.32 (CH_3-CO)
11k	1688, 1678 (amide) 1598 (Ar)	[e] 7.52-7.24 (m, 15H, 3 Ph) 1.92, 1.89 (each s, 3H, Ac)	[e] 170.31, 168.92 (C=O) 145.97 (S-C(NAcPh)=N-) 87.68 (S-CPh_2-NAc) 23.30, 23.18 (CH_3-CO)

[a]By using J-echo technique. [b]In $(CD_3)_2SO$. [c]Exchangeable for deuterium. [d]Of the benzopyran ring. [e]In $CDCl_3$.

the conversion of flavone thiosemicarbazone (**6c**) into flavone diacetylhydrazone (**6g**) may be facilitated by the formation of an intermediate flavylium salt. Such an effect of the flavone ring, resulting in different reactivity, was also indicated by the observation that flavone diacetylhydrazone (**6g**) - in contrast to the corresponding 2,3-dihydro analogue **2g** - could not be converted into the respective oxadiazoline isomer **6h** with the $Ac_2O/ZnCl_2$ reagent. Even under forcing conditions and after prolonged reaction time, the unchanged starting **6g** was almost quantitatively recovered (see Table 1).

EXPERIMENTAL

Concerning the starting materials, acetylating reagents, reaction conditions, and processing of the reaction mixtures, as well as yields and m.p. data (solvents for recrystallisation) see Table 1.

General methods of preparation

(A) The reaction mixture was poured onto ice and water.

(B) The reaction mixture was cooled. The crystals which separated were collected by suction, triturated with anhydrous ethanol-heptane 1:2, then with water, and dried.

(C) The reaction mixture was concentrated under reduced pressure (< 48°C , bath).

(D) The crystalline residue was triturated with 80% ethanol to give the crude product.

(E) The crystalline residue was triturated with anhydrous ethanol and heptane. The crude product was extracted with hot chloroform. The solution was concentrated.

(F) The residue was triturated with ice-water.

(G) A chloroform solution of the crude product was treated with fuller's earth and charcoal, then concentrated.

(H) The product was purified by column chromatography on silica gel.

(I) The product was crystallised from the solvent indicated.

4-Chromanone thiosemicarbazone (**1c**): A mixture of 4-chromanone (**1a**, 11.0 g, 74.0 mmol, Aldrich), thiosemicarbazide (13.2 g, 145 mmol), anhydrous ethanol (600 mL), and conc. HCl (3 mL) was boiled for 22 hr, then cooled to give crude (15.9 g, 97%, m.p. 208°C) or recrystallised **1c** (15.28 g, 93.3%), m.p. 215-216°C (from EtOH). Tlc (8:2 $CHCl_3$-EtOAc) R_F 0.47, (95:5 $CHCl_3$-MeOH) R_F 0.74. IR (KBr): 3435, 3235, 3160, 2988, 2884, 1605, 1515, 1507 cm^{-1}. *Anal.* Calcd for $C_{10}H_{11}N_3OS$: C, 54.28;

H, 5.01; N, 18.99; S, 14.49. Found: C, 54.41; H, 5.18; N, 18.88; S, 14.50.

trans-3-Hydroxyflavanone thiosemicarbazone (**3c**): A mixture of *trans*-3-hydroxyflavanone (**3a**[23], 3.604 g, 15 mmol), thiosemicarbazide (1.641 g, 18 mmol), anhydrous ethanol (140 mL), and conc. HCl (0.6 mL, 7 mmol) was boiled for 6 hr, then concentrated. The residue was triturated with water (~100 mL) to give crude (4.156 g, 88.4%) or recrystallised **3c** (3.387 g, 72.1%), m.p. 198-199°C (from chloroform-ethanol). Tlc (3:1 benzene-ethyl acetate) R_F 0.45. IR (KBr):3225, 1560, 1478, 1472, 1456, 1440 cm^{-1}. *Anal.* Calcd for $C_{16}H_{15}N_3O_2S$: C, 61.32; H, 4.82; N, 13.41; S, 10.23. Found: C, 61.57; H, 5.02; N, 13.29; S, 10.53.

2-Benzylidene-1-indanone thiosemicarbazone (**9c**): A mixture of 2-benzylidene-1-indanone (**9a**[21,22], 3.304 g, 15 mmol), thiosemicarbazide (2.734 g, 30 mmol), anhydrous ethanol (150 mL), and conc. HCl (0.6 mL) was boiled for 5 hr, then cooled to give crude (4.212 g, 95.7%, m.p. 213°C) or recrystallised **9c** (3.618 g, 82.2%), m.p. 219°C (dec., from ethanol). Tlc ($CHCl_3$) R_F 0.22. IR (KBr): 3340, 3232, 3144, 1635, 1600, 1570*, 1481, 1453 cm^{-1}. MS *m/e*: 293 (M^+), 275, 260, 233, 218 (100%). *Anal.* Calcd for $C_{17}H_{15}N_3S$: C, 69.59; H, 5.15; N, 14.32; S, 10.93. Found: C, 69.81; H, 5.35; N, 14.42; S, 10.98.

9-Fluorenone thiosemicarbazone (**10c**): A mixture of 9-fluorenone (**10a**, 3.678 g, 98% purity, 20 mmol), thiosemicarbazide (2.111 g, 98% purity, 22.7 mmol), and acetic acid (96%, 10 mL) was boiled for 2 hr, then cooled. The product separated was filtered off and washed successively with 50% acetic acid, water, and hexane to give crude **10c** (4.860 g, 96%), m.p. 217°C (dec.). Recrystallisation of the crude product (1.755 g) from 2-methoxyethanol (35 mL) upon addition of water (10 mL) afforded pure **10c** (1.537 g, yield 84%), m.p. 214°C (dec.). Tlc (2:1 PhH-EtOAc) R_F 0.68. *Anal.* Calcd for $CH_{14}H_{11}N_3S$: C, 66.37; H, 4.38; N, 16.59; S, 12.66. Found: C, 66.92; H, 4.60; N, 16.56; S, 12.80.

Benzophenone 4-phenylthiosemicarbazone (**11d**): A mixture of benzophenone hydrazone (**11b**, 7.850 g, 40 mmol), phenyl isothiocyanate (5.795 g, 42 mmol, purity 98%), and ethyl acetate (12 mL) was boiled for 9 hr, then cooled and diluted gradually with hexane (60 mL) to give crude (13.261 g, 100%) or recrystallised (9.849 g, 74.3%) **11d**, m.p. 154°C (from isopropanol). Tlc ($CHCl_3$): R_F 0.50. *Anal.* Calcd for $C_{20}H_{17}N_3S$: C, 72.47; H, 5.17; N, 12.68; S, 9.68. Found: C, 72.68; H, 5.24; N, 12.64; S, 9.74.

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