A NOVEL SYNTHESIS OF THIAZOLYL, IMIDAZOTHIADIAZOLYL, AND THIADIAZINYL-2*H*-1-BENZOPYRAN-2-ONES*

V. Rajeswar Rao, M. S. Rao and T. V. Padmanabha Rao

Department of Chemistry,
Kakatiya University, Warangal 506 009, India

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3-Acetylcoumarins *I* with arylthiourea in the presence of iodine gave substituted-3-(2-arylamino--4-thiazolyl)-2*H*-1-benzopyran-2-ones (*IIa—IIc*.) The structures of these products have been confirmed and they were converted into acetyl derivatives (*IId—IIf*.) Condensation of various 3-(2-bromoacetyl)-2*H*-1-benzopyran-2-ones (*III*) with 2-amino-6-substituted thiadiazoles *IV* in the presence of ethanol and dimethylformamide yielded substituted 3-(2-substituted imidazo[2,1-*b*]-thiadiazol-6-yl)-2*H*-1-benzopyran-2-ones (*VI*.) Reaction of *III* with 3-substituted 4-amino-5-mercapto-S-triazole *VII* resulted in the formation of *VIII* in a single step.

Thiazole derivatives exhibit a wide spectrum of biological activities[1-4]. S-Ttriazolothiadiazines have been shown to exhibit remarkable anthelmentic activity[5] and also coumarin derivatives with a heterocyclic system at position 3 exhibit a promising biological activity[6]. In view of this and in continuation of earlier work on the synthesis of heterocyclic systems from coumarin derivatives[7] we report herein the preparation of novel heterocyclic systems, thiazolyl, imidazothiadiazolyl and thiadiazinyl coumarins starting from 3-acetylcoumarins. Rout and coworkers[8] prepared 4-(3'--coumarinyl)-2-arylaminothiazoles by treating 3-(ω-bromoacetyl)coumarin with various arylthioureas in boiling ethanol. This involves a two step preparation and suffers from various limitations. When this procedure is applied with substituted 3-(ω-bromacetyl)coumarins and arylthioureas in the presence of ethanol a resinous mixture of products results. Some of the substituted 3-(ω-bromacetyl)coumarins are partially soluble in alcohol and it was not possible to convert them into thiazolylcoumarins. To overcome these limitations we have developed a one-step-preparation of *IIa—IIc* starting from *I*. *I*, on heating with phenylthiourea in the presence of iodine gave *IIa—IIc* in good yields. The products obtained (Tables I and II) as salts, on treatment with aqueous ammonia liberated the free bases. The structures of these compounds have been confirmed by converting them into their acetates.

All the thiazolylcoumarins displayed strong absorption bands of thiazole[9] at 1 540, 1 550, 1 605 and lactone carbonyl at 1 710 cm^{-1}. The ^1H NMR spectrum of

* Part IV in the series Studies on Coumarin Derivatives.

TABLE I

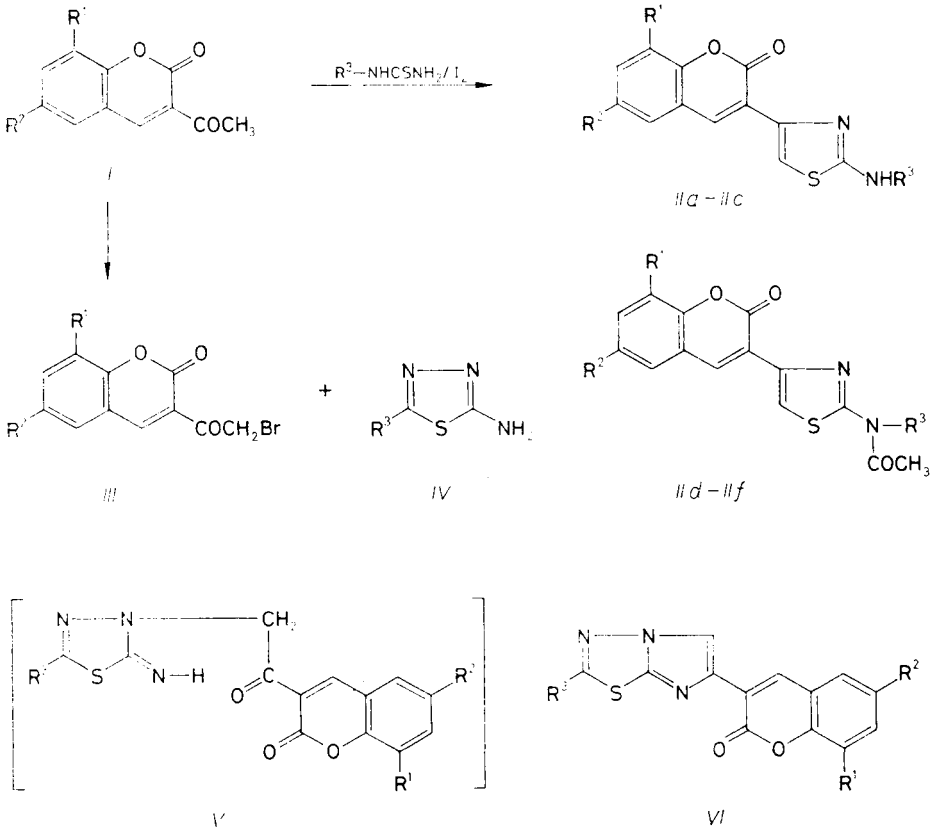
Analytical data of compounds *II* and *VI*

Compound[a]	R^1 R^2	R^3	M.p.[b] °C	Formula (M. W.)	Calculated/found		
					% C	% H	% N
IIa	H	C_6H_5	246[c]	$C_{18}H_{12}N_2O_2S$	67·50	3·75	8·75
	H			(320·5)	67·46	3·71	8·64
IIb	H	C_6H_5	255	$C_{18}H_{11}BrN_2O_2S$	54·13	2·75	7·01
	Br			(399·3)	54·10	2·78	7·00
IIc	Br	C_6H_5	245	$C_{18}H_{10}Br_2N_2O_2S$	45·18	2·09	5·85
	Br			(478·2)	45·00	2·00	5·81
IId	H	C_6H_5	258	$C_{20}H_{14}N_2O_3S$	66·29	3·86	7·73
	H			(374·4)	66·21	3·80	7·69
IIe	H	C_6H_5	260	$C_{20}H_{13}BrN_2O_3S$	54·13	2·75	7·01
	Br			(453·3)	54·10	2·71	7·00
IIf	Br	C_6H_5	305	$C_{20}H_{12}Br_2N_2O_3S$	46·15	2·30	5·38
	Br			(532·2)	46·10	2·29	5·35
VIa	H	CH_3	275	$C_{14}H_9N_3O_2S$	59·36	3·18	14·84
	H			(283·3)	59·10	3·10	14·80
VIb	H	C_2H_5	270	$C_{15}H_{11}N_3O_2S$	60·60	3·70	14·14
	H			(297·3)	60·59	3·72	14·00
VIc	H	C_3H_7	218	$C_{16}H_{13}N_3O_2S$	61·73	4·18	13·50
	H			(311·4)	61·70	4·16	13·48
VId	H	C_4H_9	116	$C_{17}H_{15}N_3O_2S$	62·76	4·61	12·92
	H			(325·4)	(62·72)	(4·60)	(12·90)
VIe	H	CH_3	194	$C_{14}H_8BrN_3O_2S$	46·40	2·20	11·60
	Br			(362·2)	(46·39)	(2·19)	(11·58)
VIf	H	CH_3	155	$C_{14}H_8ClN_3O_2S$	52·99	2·52	13·24
	Cl			(317·7)	(52·91)	(2·50)	(13·20)
VIg	H	C_2H_5	>310	$C_{15}H_{10}Br_2N_3O_2S$	47·87	2·65	11·17
	Br			(456·1)	(47·84)	(2·61)	(11·00)
VIh	H	C_3H_7	200	$C_{16}H_{12}BrN_3O_2S$	49·23	3·07	10·76
	Br			(390·2	(49·20)	(3·00)	(10·70)
VIi	H	C_4H_9	110	$C_{17}H_{14}BrN_3O_2S$	50·49	3·46	10·34
	Br			(404·3)	(50·40)	(3·42)	(10·30)
VIj	Br	CH_3	285	$C_{14}H_7Br_2N_3O_2S$	38·09	1·58	7·25
	Br			(441·1)	(38·00)	(1·52)	(7·21)
VIk	Br	C_2H_5	>340	$C_{15}H_9Br_2N_3O_2S$	39·56	1·97	9·23
	Br			(455·1)	(39·52)	(1·92)	(9·20)

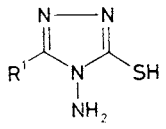
TABLE I
(*Continued*)

Compound[a]	R^1 R^2	R^3	M.p.[b] °C	Formula (M.W.)	Calculated/found % C	% H	% N
VII	Br Br	C_3H_7	180	$C_{16}H_{11}Br_2N_3O_2S$ (469·1)	40·93 (40·90)	2·34 (2·30)	8·95 (8·92)
VIm	Br Br	C_4H_9	<340	$C_{17}H_{13}Br_2N_3O_2S$ (483·2)	42·23 (42·20)	2·69 (2·60)	8·69 (8·64)
VIn	OCH_3 H	CH_3	<340	$C_{15}H_{11}N_3O_3S$ (323·4)	57·50 (57·48)	3·51 (3·50)	13·41 (13·39)

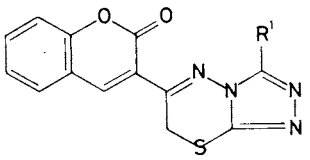
[a] Obtained in 70–80% yields; [b] crystallized from ethanol; [c] ref.[8] 248°C.



IIa–*IIc* exhibited a characteristic singlet for the thiazole proton at δ 7·85. The remaining protons were observed in the usual region (Table III). The structures of *IIa*–*IIc* were confirmed by preparing their acetyl derivatives. Derivatives *IId*–*IIf* showed strong IR-absorption band at 1 680 cm^{-1} due to —$NCOCH_3$.



VII



VIII

TABLE II

Analytical data of compounds *VIII*

Compound[a]	R^1	M.p.[b] °C	Formula (M. W.)	Calculated/found			
				% C	% H	% N	% S
VIIIa	Methyl	232	$C_{14}H_{10}N_4O_2S$ (298·3)	56·37 56·30	3·35 3·34	18·79 18·78	10·74 10·70
VIIIb	Ethyl	225	$C_{15}H_{12}N_4O_2S$ (312·4)	57·69 57·66	3·85 3·84	17·95 17·92	10·26 10·21
VIIIc	Propyl	247	$C_{16}H_{14}N_4O_2S$ (326·4)	58·89 58·85	4·29 4·25	17·18 17·10	9·82 9·80
VIIId	Phenyl	250	$C_{19}H_{12}N_4O_2S$ (360·4)	63·33 63·30	3·33 3·21	15·55 15·50	8·89 8·87
VIIIe	*p*-Tolyl	252	$C_{20}H_{14}N_4O_2S$ (374·4)	64·17 54·10	2·74 3·71	14·97 14·96	8·56 8·52
VIIIf	*m*-Tolyl	254	$C_{20}H_{14}N_4O_2S$ (374·4)	64·17 64·12	3·74 3·72	14·97 14·94	8·56 8·55
VIIIg	*o*-Chlorophenyl	205	$C_{19}H_{11}ClN_4O_2S_2$ (394·8)	57·79 57·76	2·79 2·76	14·19 14·12	8·11 8·10
VIIIh	*p*-Chlorophenyl	248	$C_{19}H_{11}ClN_4O_2S$ (394·8)	57·79 57·72	2·79 2·76	14·19 14·16	8·11 8·12
VIIIi	*p*-Nitrophenyl	249	$C_{19}H_{11}N_5O_4S$ (405·4)	56·30 56·32	2·72 2·70	17·28 17·26	7·90 7·80
VIIIj	4-pyridyl	226	$C_{18}H_{11}N_5O_2S$ (361·4)	58·83 59·80	3·05 3·00	19·39 19·35	8·86 8·82

[a] Obtained in 70–80% yields; [b] crystallized from acetic acid.

TABLE III

Spectral data of compounds *II* and *VI*

Compound	IR (ν_{max}, cm^{-1})			^1H NMR (δ, ppm)[a]	Mass spectra (m/z, %)
	—C=O	—NH—	—C=N		
IIa	1 710	3 310	1 605	7·2—7·6 (m, 9 H, Ar—H), 7·85 (s, 1 H, $C_{(5)}$—H of thiazole), 8·55 (s, 1 H, $C_{(4)}$—H of coumarin), —NH[b]—(s, 1 H, 10·86).	102 (88), 104 (62), 117 (49), 118 (34), 145 (85), 146 (65), 172 (78), 173 (70), 202 (22), 203 (26), 291 (20), 292 (10) and 320 (100)
IIb	1 720	3 315	1 610	7·0—7·5 (m, 8 H, Ar—H), 7·80 (s, 1 H, $C_{(5)}$—H of thiazole), 8·54 (s, 1 H, $C_{(4)}$—H of coumarin), —NH[b]—(s, 1 H, 10·88).	—
IIc	1 710	3 310	1 600	7·10—7·7 (m, 7 H, Ar—H), 7·82 (s, 1 H, $C_{(5)}$—H of thiazole), 8·58 (s, 1 H, $C_{(4)}$—H of coumarin), —NH[b]—(s, 1 H, 10·84).	—

	—N—$COCH_3$	—C=O	—C=N		
IId	1 680	1 715	1 605	2·1 (s, 3 H, —NC OCH_3), 7·3—7·9 (m, 9 H, Ar—H), 7·84 (s, 1 H, $C_{(5)}$—H of thiazole), 8·56 (s, 1 H, $C_{(4)}$—H of coumarin).	—
IIe	1 680	1 720	1 605	—	—
IIf	1 685	1 715	1 600	—	—
VIa	—	1 720	—	2·7 (s, 3 H, —CH_3), 7·2—7·6 (m, 4 H, Ar—H), 8·50 (s, 1 H, imidazole), 8·55 (s, 1 H, $C_{(4)}$—H of coumarin).	127 (17), 143 (78·5), 155 (80), 170 (32), 184 (79), 216 (10·5), 244 (9) and 283 (100)
VIb	—	1 715	—	1·3 (t, 3 H, —CH_2CH_3), 4·1 (q, 2 H, —CH_2CH_3), 7·24—7·68 (m, 4 H, Ar—H), 8·50 (s, 1 H, imidazole proton), 8·56 (s, 1 H, $C_{(4)}$—H of coumarin).	—
VIe	—	1 720	—	2·6 (s, 3 H, —CH_3), 7·3—7·68 (m, 3 H, Ar—H), 8·52 (s, 1 H, imidazole), 8·56 (s, 1 H, $C_{(4)}$—H of coumarin).	—

[a] In deuteriochloroform–hexadeuteriodimethyl sulfoxide for *IIa—IIc*, in deuteriochloroform for *IId—IIf*; [b] disappeared on addition of ^2H_2O.

Bromination of 3-acetylcoumarins[10] in the presence of bromine and alcohol free chloroform gave *III*. Reaction of *III* with *IV* in a mixture of anhydrous ethanol and dimethylformamide furnished *VI* in excellent yields.

A convenient one step synthesis of 3-(3-(4-substituted alkyl/aryl/heteroaryl)-7*H*--1,2,4-triazolo[3,4-*b*] [1,3,4]thiadiazin-6-yl)-2*H*-1-benzopyran-2-ones (*VIIIa* – *VIIIj*) has been achieved by a reaction of *III* with 3-alkyl/aryl/heteroaryl-4-amino-5-mercapto-S-triazoles[11,12] (*VII*) in ethanol or ethanol containing catalytic amount of pyridine. The yields from these two methods are quantitative. Various attempts have been made to isolate intermediate 3-substituted (coumarinacyl)mercapto-S-triazole but our trial did not meet with much success.

EXPERIMENTAL

All the melting points were determined in open capillary tubes using sulphuric acid bath and are uncorrected. IR spectra (ν_{max} cm^{-1}) were recorded on Perkin–Elmer-282 instrument. The ^1H NMR spectra were recorded on Varian 90 MHz spectrometer using tetramethylsilane as internal standard and chemical shifts are expressed in δ ppm. Mass spectra were scaned on a JEOL-JMS-300 spectrometer at 70 eV.

TABLE IV
Spectral data of compounds *VIII*

Compound	IR ν_{max}, (cm^{-1})		^1H NMR (δ, ppm)[a]	Mass spectra, *m/z* (%)
	—C=O	—C=N		
VIIIa	1 720	1 605	2·55 (s, 3 H, $-CH_3$), 4·15 (s, 2 H, $-S-CH_2-$), 7·35–7·80 (m, 4 H, Ar—H), 8·45 (s, 1 H, coumarin $C_{(4)}$—H)	195 (10), 171 (55), 170 (45), 143 (15), 127 (65), 105 (30), 89 (15), 298 (100)
VIIIb	1 720	1 600	1·4 (5, 3 H, $-CH_2-CH_3$), 4·0 (q, 2 H, $-CH_2-CH_3$), 4·2 (s, 2 H, $-S-CH_2$), 7·35–7·70 (m, 4 H, Ar—H), 8·50 (s, 1 H, coumarin $C_{(4)}$—H)	–
VIIId	1 715	1 510	–	–

[a] In deuteriochloroform.

3-(2-Arylamino-4-thiazolyl)-2*H*-1-benzopyran-2-ones (*IIa—IIc*)

A mixture of *I* (2 mmol), iodine (2 mmol) and phenylthiourea (4 mmol) was heated on a water bath for 24 h. The residue so obtained was washed with ether, extracted with hot water and filtered. The filtrate on treatment with dilute ammonia liberated the free base which was filtered. washed with water and crystallized, *viz.* Tables I and III.

Acetyl derivatives IId—IIf: *IIa—IIc* (2 mmol) was dissolved in minimum amount of acetic anhydride and to this was added drop of pyridine. The mixture was kept aside for 24 h at room temperature. The solid obtained was filtered, washed with cold water and crystallized, *viz.* Tables I and III.

Substituted 3-(2-Substituted Imidazo[2,1-*b*]thiadiazol-6-yl)-2*H*-1-benzopyran-2-ones (*VIa— VIn*)

A mixture containing *III* (2 mmol) and 2-amino-6-substituted thiadiazole (2 mmol) in ethanol (8 ml) and dimethylformamide (8 ml), was refluxed for 6 h, when a solid separated out. The mixture was cooled, the solid filtered, washed with water and crystallized, *viz.* Tables I and III.

3-(3-(4-Substituted Alkyl/aryl/heteroaryl)-7*H*-1,2,4-triazolo[3,4-*b*] [1,3,4]thiadiazin-6-yl)-2*H*-1-benzopyran-2-ones (*VIIIa— VIIIj*)

A mixture of substituted 3-(ω-bromoacetyl)coumarin (1 mmol) and an appropriate 3-substituted-4-amino-5-mercapto-S-triazole (*VII*) (1 mmol) in ethanol containing catalytic amount cooled, the solid was filtered, washed with water and crystallized, *viz.* Tables II and IV.

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