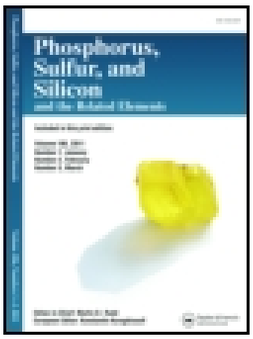

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A FACILE ONE STEP SYNTHESIS OF [3-(2-HYDRAZINO-4-THIAZOLYL) COUMARINO] DIMETHYL METHINES AND SOME 3-SUBSTITUTED-7H-6-(6/8,6,8-SUBSTITUTED-3-COUMARINO)-*S*-TRIAZOLO[3,4-b] [1,3,4]THIADIAZINES

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A FACILE ONE STEP SYNTHESIS OF [3-(2-HYDRAZINO-4-THIAZOLYL) COUMARINO] DIMETHYL METHINES AND SOME 3-SUBSTITUTED-7H-6-(6/8, 6, 8-SUBSTITUTED- 3-COUMARINO)-s-TRIAZOLO[3, 4-b][1, 3, 4]THIADIAZINES

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Some [3-(2-hydrazino-4-thiazolyl) coumarino]dimethyl methine derivatives (III) have been prepared by the condensation of 3-(2-bromoacetyl)-coumarin and thiosemicarbazide in acetone. These compounds formation was further confirmed by the condensation of acetone thiosemicarbazone (I) and p-N,N-dimethyl amino benzaldehyde thiosemicarbazone (II) with 3-(2-bromoacetyl)coumarin in anhydrous ethanol and dimethyl formamide in a two step process. 3-Substituted-7H-6-(6 or 8 or 6, 8-disubstituted 3-coumarino)-s-triazolo[3, 4-b] [1, 3, 4]thiadiazines (V) have also been prepared from simple condensation of appropriate 4-amino-5-mercapto-1, 2, 4-triazole with various 3-(2-bromoacetyl) coumarins in anhydrous ethanol and dimethyl formamide.

Keywords: Thiadiazine; thiazole; thiazolyl coumarin

INTRODUCTION

Coumarin nucleus is found in a variety of natural products which exhibit various pharmacological effects. Derivatives of coumarin also form components of important drugs having varied properties There are excellent monographs and review articles[1–5] describing the structure, synthetic reactions and properties of coumarin. Numerous reports have appeared in the literature describing antimicrobial[6,7], antiradiation[8,9] and antipara-

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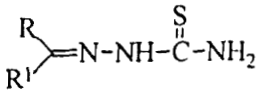
sitic [10] properties of the thiazole ring. Various 1,2,4-triazoles and N-bridged heterocycles derived from then are found to be associated with diverse pharmacological activity[11–16]. The 1,2,4-triazole nucleus has recently been incorporated into a wide variety of therapeutically interesting drugs including H_1/H_2 histamine receptor blockers, choline esterase active agents, CNS stumilants antianxiety agents and sedatives[17].

Prompted by the above observations and in continuation of our search for biologically active nitrogen and sulfur containing heterocycles[18–20] it was decided to synthesize these heterocyclic coumarins.

RESULTS AND DISCUSSION

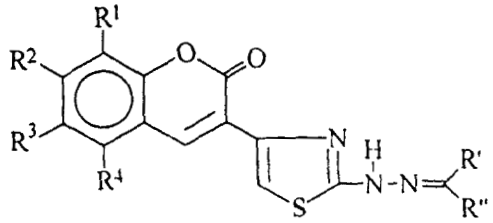
Synthesis of [3-(2-hydrazino-4-thiazolyl)coumarino]dimethyl methine (III) derivatives has been achieved by the condensation of 3-(2-bromo acetyl)coumarin, thiosemicarbazide and acetone in a single step under cold condition. The structure of these compounds were further confirmed by condensation of 3-(2-bromoacetyl)coumarins with acetone thiosemicarbazone (I) in anhydrous ethanol and dimethyl formamide. The compounds obtained by both methods are identical (by mixed m.p. measurements, Co-TLC, IR spectra). Reaction of p-N,N-dimethyl amino benzaldehyde thiosemicarbazone (II) with 3-(2-bromoacetyl)coumarin in anhydrous ethanol and dimethyl formamide resulted in the formation of [3-(2-hydrazino-4-thiazolyl coumarino]phenyl methine. All the [3-(2-hydrazino-4-thiazolyl)coumarino]dimethyl methine (III) derivatives and corresponding phenyl methine derivatives (IV) displayed characteristic absorption bands due to C=N and lactone C=O at 1608 and 1716 cm^{-1}. The ^{1}H-NMR spectra of IIIa exhibited a characteristic singlet for the thiazole and coumarin C_4-protons at δ7.9 and 8.6 respectively. The remaining protons are observed in the usual region (Table I).

The 7H-6-(6 or 8 or 6,8-substituted 3-coumarino-s-triazolo[3,4-b]-[1,3,4]thiadiazines (V) were synthesized by condensing various 4-amino-5-mercapto-1,2,4-triazoles with 3-(2-bromoacetyl)coumarins in equal volumes of anhydrous ethanol and dimethyl formamide. All the compounds displayed strong absorption bands due to -C=N- and lactone carbonyl of coumarin absorptions at 1644 and 1716 cm^{-1}. The ^{1}H-NMR spectrum of Va exhibited a characteristic singlet for $-CH_2-$ of thiadiazine at δ4.5. The remaining protons were observed in the expected regions (Table I).



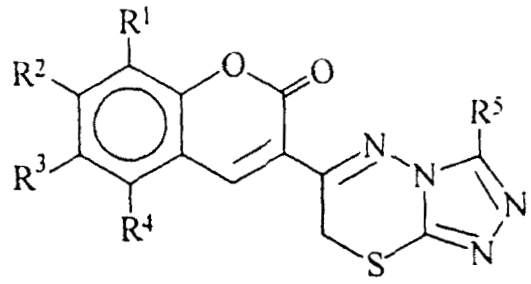
I) R = R^1 = CH_3

II) R = H, R^1 = P-Dimethyl amino phenyl



III) R' = R" = CH_3

IV) R' = H, R" = P-Dimethyl amino phenyl



(V)

TABLE I Spectral Data of Compounds

Compd	*IR-C=N*	(ν_{max} cm^{-1}) O ‖ - C-O- (lactone)	*^{1}H-NMR(δ ppm)*[a]	*Mass spectra (m/z %)*		
IIIa	1608	1722-3	2.18(s,6H, 2 × CH_3), 7.39–7.80 (m,4H Ar-H), 7.80(s,1H,C_5 of thiazole), 8.68(s,1H,C_4 of coumarin), 11.8–12.0 (b,s,1H, NH, D_2O exchangeable)	102(12), 173(22), 257(10),	145(15), 174(20), 284(85),	172(90), 243(25), 299(100%)
IIIb	1610	1722-3	2.21(s,6H, 2 × CH_3), 4.0 (s,3H,OMe), 7.16–7.40 (m,3H,Ar-H), 7.88(s,1H,C_5 of thiazole), 8.59(s,1H,C_4 of coumarin), 11.8–12.0(b,s,1H,NH,D_2O exchangeable)		---	
IV	1604	1 722-3	---	145(30), 211(20),	146(2-7), 244(100),	172(20), 390(22)
Va	1644	1718	4.5(s,2H, -S-CH_2), 7.8–8.8(m,4H, Ar-H), 8.6(s,1H, triazole), 8.8(s, 1H, C_4 of coumarin)	143(70), 188(50),	171(7.5), 203(30),	173(100), 284(10).
Vb	1644	1718	4.0(s,3H, OCH_3), 4.7(s,2H, -SCH_2), 7.15–7.35(m, 3H,Ar-H), 8.45(s, 1H, triazole) and 8.6 (s, 1H, C_4 of coumarin)		---	
Vc	-	-	4.65 (s, 2H, -SCH_2), 7.75 (d, 1H, J=2H_Z), 8.0 (d, 1H, J=2H_Z), 8.3 (s, 1H, triazole) and 8.45 (s, 1H, C_4 of coumarin)		---	
Vd	-	-	4.7 (s, 2H, -SCH_2-), 7.5 – 7.9 (m, 3H, Ar-H), 8.2 (s, 1H, triazole) and 8.7 (s, 1H, C_4 of coumarin)		---	
Vi	-	-	3.98 (s, 3H, OCH_3), 4.9 (s, 2H, -CH_2-), 7.6 (d, 1H, J=2H_Z, Ar-H), 7.8 (d, 1H, J=2H_Z, Ar-H), 8.6 (s, 1H, triazole) and 8.8 (s, 1H, C_4 of coumarin)		---	

[a]Compound IIIa, Va, Vb, is in $CDCl_3$ + DMSO-d_6, Vc, Vd and Vi is in DMSO-d_6 and IIIb in $CDCl_3$. Compound IV is insoluble in common organic solvents, hence, NMR could not be taken.

TABLE II Analytical Data of III, IV and V

Compd	R^1 R^2	R^3 R^4	R^5	*m.p.* (°C)	*Elemental Analyses – Calcd. (Found)*			
					C	*H*	*N*	*S*
IIIa	H	H		235–237	60.20	4.34	14.04	10.70
	H	H			(60.00)	(4.31)	(14.00)	(10.67)
IIIb	OMe	H		220–222	58.35	4.55	12.76	9.72
	H	H			(58.31)	(4.52)	(12.73)	(9.70)
IIIc	H	Br		255–257	47.61	3.14	11.11	8.46
	H	H			(47.58)	(3.14)	(11.10)	(8.43)
IIId	Br	Br		205–207	39.38	2.40	9.19	7.00
	H	H			(39.35)	(2.20)	(9.16)	(7.00)
IIIe	OCH_3	NO_2		219–221	56.14	4.09	16.37	9.35
	H	H			(56.13)	(4.00)	(16.33)	(9.31)
IIIf	H	H		244–246	57.14	4.12	13.33	10.15
	OH	H			(57.11)	(4.10)	(13.30)	(10.12)
IIIg	Br	Br		225–227	38.05	2.32	8.87	6.73
	OH	H			(38.00)	(2.30)	(8.84)	(6.70)
IIIh	H	Cl		240–242	53.97	3.59	12.59	9.59
	H	H			(53.94)	(3.54)	(12.53)	(9.55)
IIIi	Cl	Cl		236–238	48.91	2.98	11.21	8.69
	H	H			(48.90)	(2.95)	(11.20)	(8.66)
IVa	H	H		265–267	64.12	5.34	14.24	8.14
	H	H			(64.00)	(5.31)	(14.20)	(8.10)
Va	H	H	H	168–170	54.92	2.81	19.71	11.26
	H	H			(54.91)	(2.78)	(19.68)	(11.23)

Compd	R^1 R^2	R^3 R^4	R^5	*m.p.* (°C)	*Elemental Analyses – Calcd. (Found)*			
					C	*H*	*N*	*S*
Vb	OCH_3	H	H	115–117	53.50	3.18	17.83	10.19
	H	H			(53.46)	(3.14)	(17.80)	(10.14)
Vc	Br	Br	H	85–87	35.29	1.35	12.66	7.23
	H	H			(35.25)	(1.32)	(12.63)	(7.21)
Vd	H	Cl	H	110–112	18.97	2.19	17.58	10.04
	H	H			(18.96)	(2.16)	(17.55)	(10.00)
Ve	Cl	Cl	H	198–200	44.19	1.69	15.86	9.06
	H	H			(44.15)	(1.65)	(15.83)	(9.00)
Vf	C_4H_4	H	H	115–117	61.07	2.99	16.76	9.58
		H			(61.00)	(2.96)	(16.73)	(9.54)
Vg	H	H	H	123–125	54.93	2.81	19.71	11.26
	OH	H			(54.90)	(2.80)	(19.68)	(11.23)
Vh	Br	Br	H	145–147	35.29	1.35	12.67	7.23
	OH	H			(35.25)	(1.31)	(12.62)	(7.20)
Vi	OCH_3	Br	H	123–125	44.56	2.38	14.85	8.48
	H	H			(44.52)	(2.34)	(14.81)	(8.46)
Vj	OMe	NO_2	H	135–137	48.90	2.62	20.40	9.32
	H	H			(48.86)	(2.60)	(20.36)	(9.30)

Compounds IIIa-IIIi were recrystallized from MeOH. Compounds IVa,Va to Vj were recrystallized from Ag.DMF. All compounds were obtained in 70–85% yield

EXPERIMENTAL

All melting points were determined in open capillary tubes using sulfuric acid both and are uncorrected. IR spectra (υ_{max} cm^{-1}) were recorded on Perkin Elmer-282 instrument. The ^{1}H-NMR spectra were recorded on a varian 200 MHz spectrometer using tetramethyl silane as internal standard chemical shift values are expressed in δ ppm. Mass spectra were scanned on a Jeol-JMS-300 spectrometer at 70 eV. The purity of compounds was monitered by TLC performed on silicagel plates (Merck) using benzene and acetone (3:1) solvent.

The 4-amino-5-mercapto-1, 2, 4-triazole[21] and 3-(2-bromoacetyl) coumarins[22] were prepared according to the literature procedure.

Synthesis of [3-(2-hydrazino-4-thiazolyl)coumarino]dimethyl methine (IIIa)

A mixture of 3-(2-bromoacetyl)coumarin (0.01 mol) and thiosemicarbazide (0.01 mol) was taken in 20 ml of acetone and stirred for 5 minutes at room temperature. The solid separated was filtered and recrystallized viz. Table I.

Alternative synthesis of IIIa

A mixture of acetone thiosemicarbazone (0.01 mol) and 3-(2-bromoacetyl)coumarin (0.01 mol) was refluxed in an equal volumes of anhydrous ethanol and DMF for 30 minutes. The resulting solid was filtered and recrystallized viz. Table I.

Synthesis of [3-(2-hydrazino-4-thiazolyl)coumarino]-p-N,N-dimethylamino phenyl methine (IVa)

A mixture of N,N-dimethyl amino benzaldehyde thiosemicarbazone (II, 0.01 mol) and 3-(2-bromoacetyl) coumarin (0.01 mol) in anhydrous ethanol and dimethyl formamide was refluxed for 30 minutes. The solid separated was filtered and crystallized viz. Table I.

Synthesis of 7H-6-(6 or 8 or 6, 8-substituted-3-coumarino)-s-triazolo-[3,4-b][1,3,4]thiadiazines (V)

An equimolar mixture of 4-amino-5-mercapto-1, 2, 4-triazole (0.01 mol) and 3- (2-bromoacetyl) coumarin (0.01 mol) in anhydrous ethanol and dimethyl formamide (10 ml each) was heated under reflux for 2 hours. The reaction mixture was then cooled to room temperature. The precipitated triazolothiadiazines were collected by filtration washed with ethanol, dried and recrystallized viz. Table I.

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