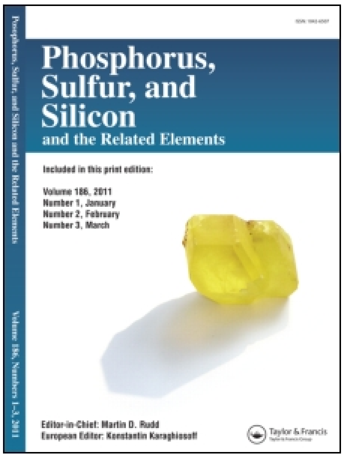

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HETEROCYCLIC SYSTEMS CONTAINING BRIDGE HEAD NITROGEN ATOM: REACTION OF 5-MERCAPTO-4*H*-IMIDAZO[4,5-*e*]-[2,1,3]BENZOTHIADIAZOLES AND 5,6-DIAMINO[2,1,3]BENZOTHIAZOLE WITH 3-(2-BROMOACETYL)COUMARINS

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*Condensation of 5-mercapto-4*H*-imidazo[4,5-*e*][2,1,3]benzothiadiazole (I) with various 3-(2-bromoacetyl)coumarins, followed by PPA cyclization of the intermediate ketones II, yielded 3-(2,8-dithia 1,3,5b, 9-tetraaza cyclopenta(b)-as-indacen-6-yl)chromen-2-ones III. Reaction of 5,6-diamino[2,1,3]benzothiadiazole with 3-(2-bromoacetyl)-coumarin in anhydrous ethanol containing fused sodium acetate gave the corresponding 2-coumarinyl 3,4-dihydro-1,4-pyrazino[5,6-e][2,1,3]benzothiadiazoles IV.*

Keywords: 3-(2-Bromoacetyl)coumarin; imidazobenzothiadiazole; pyrazine

INTRODUCTION

Benzothiadiazoles have been broadly applied in the area of pharmaceutical, agricultural, industrial, and polymer chemistry. Several of them are reported to be excellent insecticide synergists together with carbaryl.[1] A few derivatives possess sedative and hypnotic actions and are comparable to benzothiadiazipines.[2] A good number of imidazothiadiazoles have been patented as potential insecticides, herbicides,[3] and fungicides.[4] Many imidazobenzothiazoles have been used for making cyanine dyes.[5] 2-Mercapto-benzimidazoles and their derivatives have been reported to possess a wide range of physiological and industrial applications.[6–8] However, the synthesis of 5-substituted heteroaryl

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mercapto-4H-imidazo[4,5-e][2,1,3]benzo-thiadiazoles does not seem to have been reported so far.

Benzothiadiazoles are found to be associated with various biological and pharmacological activities. A good number of 2,1,3-benzothiadiazole derivatives exhibited antimicrobial activity.[9] Various derivatives of dihydropyrazines are reported to be potential antimalarial and antibacterial agents.[11,12]

Coumarin derivatives are well known for their anticoagulant, antifungal, diuretic, firinocytic, and antitubercular activities.[13] Among the various heterocyclic systems linked to the 3-position of the coumarin ring, pyridyl-coumarins have been reported as CNS depressants[14] and antimicrobial agents.[15]

A combination of benzimidazothiazole system and the coumarin ring was thought to be of interest in view of the fact that the pyrone ring is known to be hydrolysed in animals,[16] resulting in the formation of carboxyl group. The resulting compounds would be isosteric with thiazole-4-acetic acids,[17] which are known for their inflammation-inhibiting effect. Hence, the synthesis of these heterocycles was undertaken.

RESULTS AND DISCUSSION

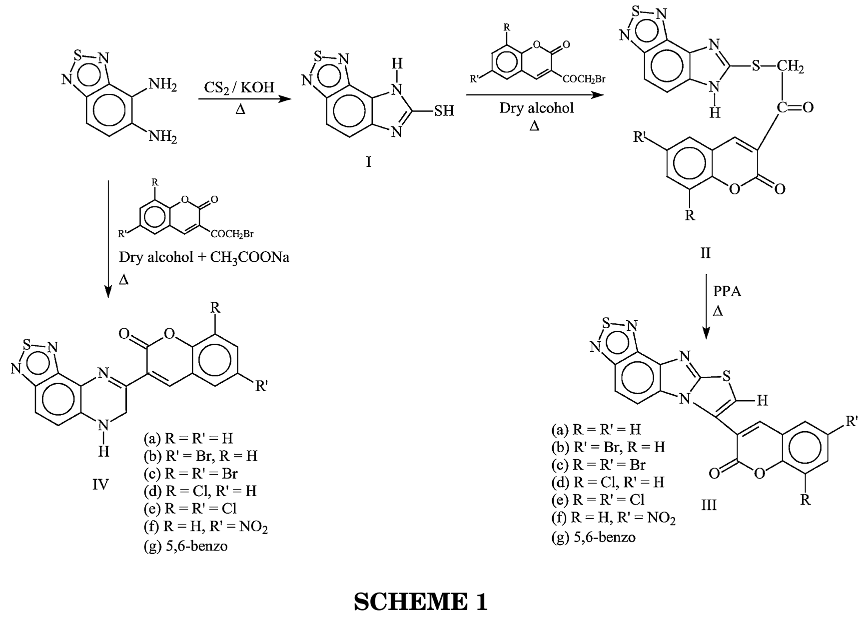
5-Mercapto-4*H*-imidazo[4,5-*e*][2,1,3]benzothiadiazole (I) has been prepared by the cyclization of 4,5-diamino-2,1,3-benzothiadiazole with carbon disulphide in presence of alcoholic potassium hydroxide.[18] The diamine, i.e., 4,5-diamino[2,1,3]benzothiadiazole, was synthesized by the amination of 4-nitro-2,1,3-benzothiadiazole with hydroxylamine hydrochloride in methanolic potassium hydroxide, followed by subsequent reduction with sodium hydrosulphite.[19] The reaction of 5-mercapto-4*H*-imidazo[4,5-*e*][2,1,3]-benzothiadiazole (**I**) with various 3-(2-bromoacetyl)coumarins in methanol containing dimethyl formamide under anhydrous conditions afforded a series of the respective 3-[2-(6*H*-imidazo[4′,5′-3,4]benzo[1,2-*c*][1,2,5]thiadiazol-7-ylsulphanyl)acetyl]chromen-2-ones (**II**). These compounds on cyclization in polyphosphoric acid gave corresponding cyclized products **III**. All of the uncyclized compounds **II** displayed characterisitic absorption bands in the IR due to 1678 (ketonic), 1720 (lactone –C=O), and 3582 cm^{-1} (—NH—) groups. The ^{1}H NMR spectra of IIa exhibited a characteristic singlet for methylene and C_4 protons of coumarin at δ 4.90 and δ 8.60, respectively. The remaining protons were observed in the usual regions. All of the cyclized compounds displayed strong absorption bands due to —C=N— and the lactone carbonyl at 1606 and 1720 cm^{-1}, respectively. Examination of IR spectra of cyclized compounds **III** have shown that there is a slight decrease in the wave number values of lactone –C=O when compared to lactone –C=O of uncyclized compounds **II**. This decrease may be attributed due to the conjugation in **III**. This is further supported by earlier observation on similar types of compounds.[20] The ^1H NMR spectra of **IIIa** exhibited a characteristic singlet for the imiazothiazole proton and C_4 proton of coumarin at δ 8.51 and δ 8.61, respectively.

Various 3-coumarinyl-3,4-dihydro-1,4-pyrazino[5,6-*e*][2,1,3]benzothiadiazoles IV were prepared by the reaction of 5,6-diamino-[2,1,3]benzodiazoles vise refluxing in anhydrous ethanol containing fused sodium acetate with different 3-(2-bromoacetyl)coumarins. The cyclized compounds **IV** exhibited —NH— absorptions in the region of 3232–3350 cm^{-1}; (broad) stretching of —C=N— is observed in the region of 1610 cm^{-1}. Absorptions at 1228 cm^{-1} are due to C—N—C systems. The lactone carbonyl absorptions are found in the region of 1720 cm^{-1}.

The PMR spectra of **IV** exhibited a characteristic singlet for —CH_2— of pyrazine at δ 4.80. The remaining protons were observed in the expected regions.

EXPERIMENTAL

All melting points were determined in open capillary tubes using a sulphuric acid bath and were uncorrected. IR spectra (ν_{max}, cm^{-1}) were



SCHEME 1

TABLE I Physical Data of Compounds **(II a–g)**

Compd.*	R R′	m.p. (°C)	Yield (%)	Mol. formula (Mol. wt.)	Found (calc.), %			
					C	H	N	S
IIa	H	225–227	89	$C_{18}H_{10}N_4O_3S_2$	54.50	2.49	14.19	16.20
	H			(394)	(54.53)	(3.05)	(14.13)	(16.18)
IIb	Br	185–187	91	$C_{18}H_9N_4BrO_3S_2$	45.70	2.30	11.82	13.51
	H			(473)	(45.48)	(2.33)	(11.79)	(13.49)
IIc	Br	230–232	92	$C_{18}H_8N_4Br_2O_3S_2$	39.25	1.79	10.15	11.60
	Br			(552)	(39.00)	(1.82)	(10.11)	(11.57)
IId	Cl	222–224	91	$C_{18}H_9N_4ClO_3S_2$	50.37	2.07	13.00	14.90
	H			(428.5)	(50.40)	(2.10)	(13.06)	(14.93)
IIe	Cl	235–237	86	$C_{18}H_8N_4Cl_2O_3S_2$	46.48	2.18	12.00	13.80
	Cl			(463)	(46.46)	(2.17)	(12.09)	(13.78)
IIf	H	238–240	91	$C_{18}H_9N_5O_5S_2$	49.18	2.00	15.92	14.54
	NO_2			(439)	(48.98)	(2.05)	(15.86)	(14.53)
IIg	5,6-Benzo	230–232	90	$C_{22}H_{12}N_4O_3S_2$	59.11	312	12.60	14.39
				(444)	(59.18)	(3.16)	(12.55)	(14.36)

*All the compounds were recrystallized from DMF + methanol.

recorded on a Perkin-Elmer spectrophotometer. The ^{1}H NMR spectra were recorded on a Varian 200 MHz unit, and the chemical shifts were recorded in δ (ppm) using tetramethyl silane (TMS) as an internal standard. The mass spectra are scanned on Jeol-JMS 300 spectrometer at 70 eV.

TABLE II Physical Data of Compounds **(III a–g)**

Compd.*	R R′	m.p. (°C)	Yield (%)	Mol. formula (Mol. wt.)	Found (calc.), %			
					C	H	N	S
IIIa	H	208–210	87	$C_{18}H_8N_4O_2S_2$	57.40	2.10	14.84	17.00
	H			(376)	(57.44)	(2.12)	(14.89)	(17.02)
IIIb	Br	234–236	89	$C_{18}H_7N_4BrO_2S_2$	47.43	1.52	12.30	14.00
	H			(455)	(47.48)	(1.54)	(12.31)	(14.09)
IIIc	Br	238–240	93	$C_{18}H_6N_4Br_2O_2S_2$	40.56	1.06	10.50	12.00
	Br			(534)	(40.60)	(1.12)	(10.52)	(12.03)
IIId	Cl	212–216	92	$C_{18}H_7N_4ClO_2S_2$	52.58	1.67	13.65	15.54
	H			(410.5)	(52.61)	(1.70)	(13.64)	(15.59)
IIIe	Cl	218–220	91	$C_{18}H_6N_4Cl_2O_2S$	48.50	1.30	12.54	14.34
	Cl			(445)	(48.53)	(1.34)	(12.58)	(14.38)
IIIf	H	228–232	87	$C_{18}H_7N_5O_4S_2$	51.00	1.62	16.60	15.18
	NO_2			(421)	(51.30)	(1.66)	(16.62)	(15.20)
IIIg	5,6-Benzo	238–240	88	$C_{22}H_{10}N_4O_2S_2$	61.93	2.30	13.10	15.00
				(426)	(61.96)	(2.34)	(13.14)	(15.02)

*All the compounds were recrystallized from DMF + CH_3OH.

The 5-mercapto-4*H*-imidazo[4,5-*e*][2,1,3]benzothiadiazole,[18] 3-(2-bromoacetyl)coumarins[21] were prepared according to the literature procedure.

3-[2-(6*H*-Imidazo[4′,5′-3,4]benzo[1,2-*c*][1,2,5]thiadiazol-7-yl sulphanyl]acetyl]chromen-2-one (IIa)

A mixture of 5-mercapto-4*H*-imidazo[4,5-*e*][2,1,3]benzothiadiazole (I, 0.01 mole) and 3-(2-bromoacetyl)coumarin (0.01 mole) was refluxed in a mixture of anhydrous ethanol and dimethyl formamide for 4 h. The reaction mixture was cooled to room temperature. The solid separated was filtered, washed with water, and recrystallized (Table I).

3-[2,8-Dithia-1,3,5b,9-tetrazacyclopenta(b)-as-indacen-6-yl)chromen-3-one (IIIa)

A mixture of ketone II (1 g), phosphorous pentoxide (4 g), and orthophosphoric acid (3 ml) was heated in an oil bath at 150°C for 4 h. The reaction mixture was cooled to room temperature, poured into water, and neutralized with potassium carbonate. The solid obtained was crystallized (Table II).

TABLE III Physical Data of Compounds **(IV a–g)**

Compd.*	R R′	m.p. (°C)	Yield (%)	Mol. formula (Mol. wt.)	Found (calc.), %			
					C	H	N	S
IVa	H	189–191	88	$C_{17}H_{10}N_4O_2S$	61.00	2.96	16.72	9.54
	H			(334)	(61.07)	(2.99)	(16.76)	(9.58)
IVb	Br	195–197	92	$C_{17}H_9BrN_4O_2S$	51.00	4.24	12.50	7.15
	H			(413)	(51.01)	(4.28)	(12.52)	(7.17)
IVc	Br	190–192	89	$C_{17}H_8Br_2N_4O_2S$	43.32	3.40	10.62	6.00
	Br			(492)	(43.37)	(3.44)	(10.65)	(6.09)
IVd	Cl	186–188	87	$C_{17}H_9CIN_4O_2S$	55.30	2.40	15.13	8.64
	H			(368.5)	(55.35)	(2.44)	(15.19)	(8.68)
IVe	Cl	218–220	90	$C_{17}H_8Cl_2N_4O_2S$	50.28	2.46	13.85	7.90
	Cl			(403.0)	(50.38)	(2.49)	(13.82)	(7.91)
IVf	H	228–230	85	$C_{17}H_9N_5O_4S$	53.50	2.90	18.32	8.40
	NO_2			(379)	(53.54)	(2.91)	(18.36)	(8.41)
IVg	5,6-Benzo	216–218	95	$C_{21}H_{12}N_4O_2S$	65.61	3.10	14.55	8.30
				(384)	(65.62)	(3.12)	(14.58)	(8.33)

*All the compounds were recrystallized from alcohol.

TABLE IV Spectral Data of Compounds **II**, **III** and **IV**

	IR ($\nu_{\max}$ cm^{-1})					
Compd.	—C═N	>C═O (lactone)	NH	>C═O	^{1}H NMR (δ ppm)	Mass spectra (m/z %)
IIa	1600	1720	3582	1678	4.90 (s, 2 H, —CH_2), 7.30–7.80 (m, 6 H, Ar-H & one NH protons), and 8.60 (s, 1 H, C_4 of coumarin)	173 (100), 188 (47.5), 208 (68.4), 376 (15.8), 394 (1.9)
IIc	1605	1737	3580	1675	4.75 (s, 2 H, —CH_2—), 7.50–7.90 (m, 4H, Ar-H & one NH protons), and 8.50 (s, 1 H, C_4 of coumarin)	—
IIe	1610	1739	3580	1680	4.8 (s, 2 H, —CH_2), 7.50–7.90 (m, 4H, Ar-H & 1 H, NH), and 8.50 (s, 1 H at C_4 of coumarin)	—
IIIa	1606	1720	—	—	7.46–8.00 (m, 6 H, Ar-H), 8.51 (s, 1 H, imidazole thiazole proton), and 8.64 (s, 1 H, C_4 of coumarin)	142 (14.4), 209 (50.1), 3.48 (27.2), 376 (100) 377 (42.7)
IIIc	1610	1735	—	—	7.60–8.00 (m, 4 H, Ar-H), 8.2 (s, 1 H, imidazothiazole), and 8.40 (s, 1 H, C_4 of coumarin)	—
IIIe	1610	1728	—	—	7.6–8.0 (m, 4 H, Ar-H), 8.2 (s, 1 H imidazole thiazole protons), and 8.40 (s, 1 H, C_4 of coumarin)	—
IVa	1610	1720	3232–3350 (broad)		4.20 (s, 2 H, —CH_2—), 6.6–8.3 (m, 7 H, 6 Ar-H and 1 NH), and 9.1 (s, 1 H, C4 of coumarin)	143 (10), 166 (16), 265 (118), 27 (54), 304 (46), 332 (100), 333 (24), and 334 (12)

2-Coumarinyl-3,4-dihydro-1,4-pyrazino[5,6-*e*][2,1,3]-benzothiadiazole (IV): General Procedure

3-(2-Bromoacetyl)coumarin (0.01 mole) was condensed with 4,5-diamino-(2,1,3)benzothadiazole (0.01 mole) in dry alcohol (50 ml) containing anhydrous sodium acetate (0.01 mole). The resultant mixture was refluxed for 6 h. It was filtered to remove sodium acetate. The excess of alcohol was distilled off. The residue was diluted with ice-cold water (100 ml). The solid that separated was filtered, washed, dried, and recrytallized from a suitable solvents (Table III).

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