FACILE SYNTHESIS OF SOME NEW 3-(2-(1,3-BENZOXAZIN-3-YL)-4-THIAZOLYL COUMARINS

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Abstract : 3-(2-Substituted benzalimino-4-thiozolyl)-coumarins (**1**) on reduction with $NaBH_4$ resulted in the formation of corresponding 3-(2-o-hydroxy benzyl hydrazino-4-thiazolyl)coumarins (**2**). These on condensation with formaldehyde gave the cycloproducts 3-(2-(1,3-benzoxazin-3-yl)-4-thiazolyl)coumarins (**3**).

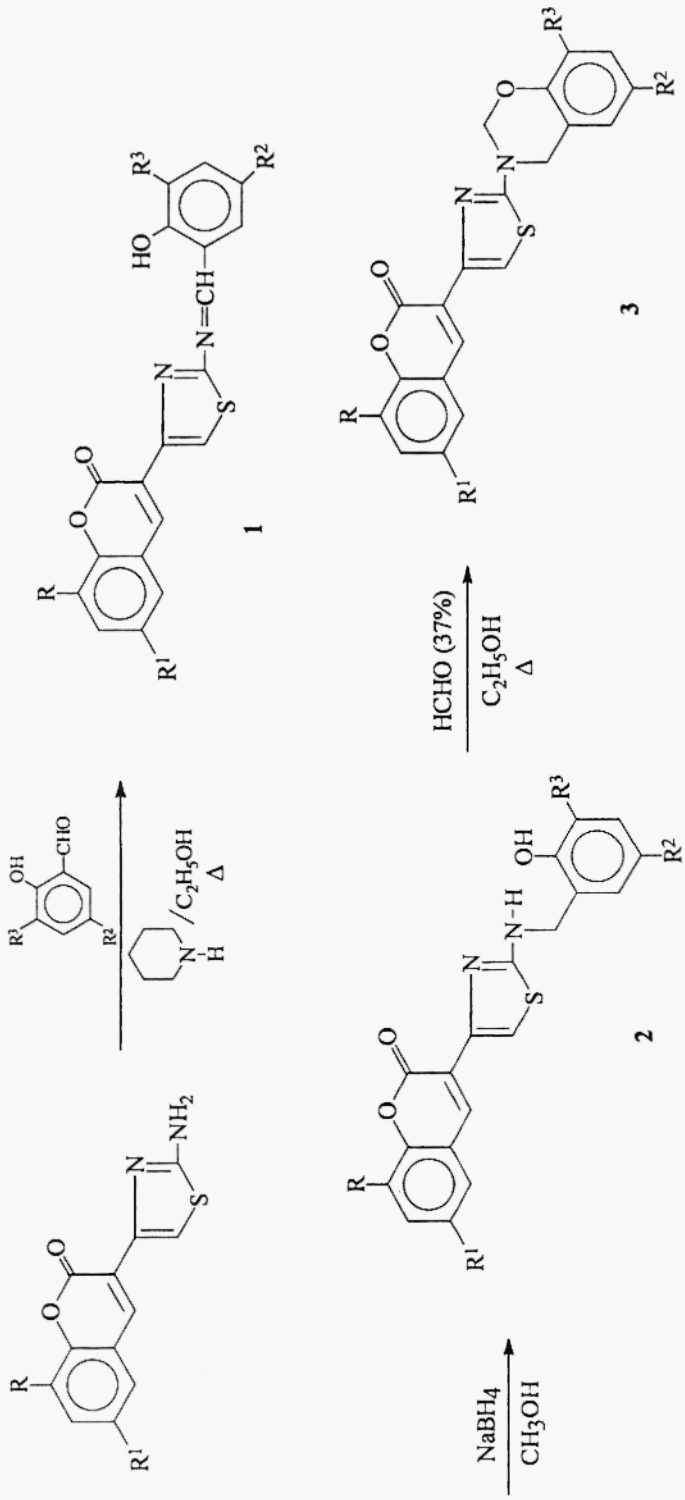
Introduction

Coumarin nucleus is found in a variety of natural products which inhibit various pharmacological effects. Derivatives of coumarin also form compounds of important drugs having varied properties. There are excellent monographs and reviews 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 antiparasitic[10] properties of the thiazole ring. Several 1,3-benzoxazine derivatives reported in the literature were found to possess antireserpine, analgesic, antiinflammatory, tranquilizing, sedative, bactericidal, bacteriostatic,[11-13] smooth muscle relaxant and spermicidal activities.[14,15] They are also used in the preparation of polymers.[16] These compounds can be prepared in one-step by Mannich reaction of a primary amine with the appropriate phenol in presence of excess of formaldehyde. However, the yields in this method are some what less. Besides, some other methods for the preparation of these compounds are reported.[17,18]

Prompted by the above observations and in continuation of our search for biologically active nitrogen and sulphur heterocyclics[19,20] it was decided to synthesize these heterocyclic coumarins.

Results and Discussions

Realising the importance of 1,3-benzoxazines during investigations on internal Mannich reactions, we tried to develop a new route for the synthesis of the title compounds **3**. The starting compound 3-(2-amino-4-thiazolyl)coumarins were prepared according to the procedure described in the literature.[21] 3-(2-o-hydroxybenzalimino-4-thiazolyl)coumarins (**1**) have been obtained by condensation of 3-(2-amino-4-thiazolyl)courmain with aromatic aldehydes. These compounds (**1**) on reduction with sodium borohydride in methanol gave 3-(2-o-hydroxy benzylamino-4-thiazolyl)coumarins (**2**). Compounds **2** under went internal Mannich reaction when refluxed with formaldehydes (37%) in ethanol for 4-5 hours to give desired 3-(2-(1,3-benzoxazin-3-yl)-4-thiazolyl coumarins **3** in excellent yields (scheme-1). The structures of newly synthesized compounds have been confirmed by analytical (Table-1) and spectral data (IR, ^1H NMR and Mass).



Scheme - 1

TABLE - 1: Analytical data of the compounds 1, 2 and 3

Compd*	R	R^1	R^2	m.p	Recryst.	Yield	Molecular formula (mol. wt.)	Calcd (Found) (%)			
			R^3	(°C)	from			C	H	N	S
1a	H	H	H	192 - 194	CH_2Cl_2	78	$C_{19}H_{12}N_2O_3S$	65.51	3.44	8.04	9.19
			H				(348)	(65.46)	(3.40)	(8.00)	(9.16)
1b	H	H	Br	252 - 54	ClC_3	80	$C_{19}H_{11}BrN_2O_3S$	53.39	2.57	6.55	7.19
			H				(427)	(53.36)	(2.53)	(6.51)	(7.45)
1c	H	H	Br	260 - 62	DMF +	76	$C_{19}H_{10}Br_2N_2O_3S$	45.05	1.97	5.55	6.32
			Br		$CHCl_3$		(506)	(44.95)	(1.96)	(5.51)	(6.30)
1d	H	H	Cl	265 - 67	$CHCl_3$	77	$C_{19}H_{11}ClN_2O_3S$	59.63	2.87	7.32	8.36
			H				(382.5)	(59.57)	(2.84)	(7.30)	(8.32)
1e	H	H	5,6-Benzo	277-78	DMF + $CHCl_3$	78	$C_{23}H_{14}N_2O_3S$ (398)	69.34 (69.31)	3.51 (3.50)	7.63 (7.61)	8.04 (8.00)
1f	H	Br	H	244 - 26	DMF +	75	$C_{19}H_{11}BrN_2O_3S$	53.39	2.57	6.55	7.49
			H		$CHCl_3$		(427)	(53.35)	(2.54)	(6.51)	(7.47)
1g	Br	Br	H	246 - 68	DMF +	70	$C_{19}H_{10}Br_2N_2O_3S$	45.05	1.97	5.53	6.32
			H		CHC_3		(506)	(45.00)	(1.95)	(5.50)	(6.30)
1h	H	Cl	H	242 - 44	DMF +	74	$C_{19}H_{11}ClN_2O_3S$	59.63	2.87	7.32	8.36
			H		$MeCl_2$		(382.5)	(59.55)	(2.84)	(7.30)	8.34
2a	H	H	H	228 - 30	CHC_3	80	$C_{19}H_{14}N_2O_3S$	65.10	3.98	8.0	9.10
			H				(350)	(65.14)	(4.0)	(8.0)	(9.14)
2b	H	H	Br	247 - 48	ClC_3	75	$C_{19}H_{12}N_2BrO_3S$	53.14	3.00	6.50	7.42
			H				(429)	(53.18)	(3.03)	(6.52)	(7.45)
2c	H	H	Br	241 - 42	$CHCl_3$	70	$C_{19}H_{12}N_2Br_2O_3S$	44.86	2.53	5.50	6.26
			Br				(508)	(44.88)	(2.56)	(5.51)	(6.29)
2d	H	H	Cl	250 - 252	$CHCl_3$ +	72	$C_{19}H_{13}ClN_2O_3S$	59.20	3.36	7.24	8.30
			H		MeOH		(384.5)	(59.29)	(3.38)	(7.28)	(8.32)
2e	H	H	5,6-Benzo	216 - 18	DMF + $CHCl_3$	74	$C_{23}H_{16}O_3N_2S$ (400)	68.99 (69.0)	4.0 (4.0)	6.96 (7.0)	8.00 (8.0)
2f	H	Br	--	224 - 26	DMF +	75	$C_{19}H_{13}NBrO_3S$	53.17	3.00	6.50	7.41
					$CHCl_3$		(428.9)	(53.15)	(3.03)	(6.52)	(7.45)

Compd*	R	R^1	R^2 R^3	m.p. (°C)	Recryst. form	Yield	Molecular formula (mol.wt.)	Calcd (Found) (%) C	H	N	S
2g	Br	Br	--	250 - 52	DMF + $CHCl_3$	79	$C_{19}H_{12}N_2Br_2O_3S$ (508)	44.86 (44.88)	2.52 (2.56)	5.50 (5.51)	6.26 (6.29)
2h	H	Cl	--	219 - 21	DMF + $CHCl_3$	70	$C_{19}H_{13}ClN_2O_3S$ (384.5)	59.25 (59.29)	3.34 (3.38)	7.25 (7.23)	8.29 (8.32)
3a	H	H	H H	166 - 68	CH_2Cl_2 + MeOH	70	$C_{10}H_{14}N_2O_3S$ (362)	66.26 (66.29)	3.85 (3.86)	7.70 (7.73)	8.80 (8.83)
3b	H	H	Br H	220 - 22	CH_2Cl_2 + MeOH	68	$C_{10}H_{13}Br_2N_2O_3S$ (441)	54.38 (54.42)	2.90 (2.94)	6.30 (6.34)	7.23 (7.25)
3c	H	H	Br Br	226 - 28	DMF + $CHCl_3$	65	$C_{20}H_{12}N_2Br_2O_3S$ (520)	45.10 (45.15)	2.27 (2.30)	5.34 (5.38)	6.14 (6.15)
3d	H	H	Cl H	224 - 26	$CHCl_3$ + MeOH	64	$C_{20}H_{13}ClN_2O_3S$ (395.5)	60.50 (60.52)	3.24 (3.27)	7.00 (7.05)	8.00 (8.07)
3e	H	H	5,6-Benzo	207 - 09	DMF + $CHCl_3$	62	$C_{14}H_{16}N_2O_3S$ (412)	69.88 (69.90)	3.85 (3.88)	6.74 (6.79)	7.73 (7.76)
3f	H	Br	--	228 - 30	DMF + $CHCl_3$	67	$C_{20}H_{13}N_2BrO_3S$ (441)	54.40 (54.42)	2.92 (2.94)	6.32 (6.34)	7.22 (7.25)
3g	Br	Br	--	226 - 28	DMF + $CHCl_3$	60	$C_{20}H_{12}N_2Br_2O_3S$ (520)	45.10 (45.15)	2.29 (2.30)	5.36 (5.38)	6.12 (6.15)
3h	H	Cl	--	160 - 62	DMF + $CHCl_3$	66	$C_{20}H_{13}ClN_2O_3S$ (395.5)	60.50 (60.52)	3.25 (3.27)	7.00 (7.05)	8.00 (8.07)

for NH group and the peak at 1723 is for lactone carbonyl. The IR spectra of all the final products do not exhibit bands in the region 3400-3450 and 3290-3299 indicating the lack of OH and -NH- functionalities. This also conforms the cyclisation of these groups with formaldehyde.

The ^{1}H NMR spectra of all the compounds **2a-2h** having hydroxy group at second position exhibits a singlet at δ 10 and a characteristic singlet is observed at δ 4.55-4.60 due to methylene hydrogens adjacent to -NH-. In the final products (**3a-3h**) there is a singlet at 4.81 due to methylene protons of -N-CH_2-O-. In the mass spectra of all the compounds **2a-2h** and **3a-3h**, molecular ion peaks are in accordance with their molecular weights.

Experimental

All melting points are uncorrected. IR spectra (ν_{max} cm^{-1}) were recorded on Perkin-Elmer 282 instrument. The ^{1}H NMR spectra were recorded on varian dpx 200 MHz spectrometer using TMS as internal standard and chemical shifts are expressed in δ ppm. Mass spectra were scanned on Jeol-JMS-300 spectrometer using 70 eV. The purity of the compounds were monitored by TLC.

3-(2-o-Hydroxybenzalimino-4-thiazolyl)coumarins (1):

A mixture of 0.001 mol of 3-(2-amino-4-thiazolyl)coumarin and appropriate o-hydroxy benzaldehyde (0.001 mol) was refluxed in ethanol containing catalytic amount of piperidine for 4 hours. The reaction mixture was cooled and the separated solid was filtered and crystallized from a appropriate solvent to yield title compounds.

3-(2-o-Hydroxybenzylamino-4-thiazolyl)coumarin (2)

Sodiumborohydride (0.085 mol) was added to a solution of compound **1** (0.002 mol) in methanol (15ml) and the mixture was stirred for 45 minutes at room teperature. The residue separated on pouring the solution into coldwater was filtered, washed withwater,dried and crystallised from suitable solvent to yield 70-80% of the title compound.

2a : m.p. 228-230°C, yield 80%, IR (ν_{max}, cm^{-1}); 1585 (-C=N-) and 1723 (OCO), 3299 (-NH-), 3400-3450 (OH), ^{1}H NMR (DMSO-d_6) (δ ppm), 4.60 (s, 1H, -CH_2-), 6.75 - 7.75 (m, 10H, Ar-H including 1H of thiazole and 1H, NH), 8.55 (s, 1H, C_4 of coumarin) and 10.0 (s, 1H (br), OH phenolic, D_2O exchangeable).
2h : 219-21°C, yield 70%, IR (ν_{max}, cm^{-1}); 1585 (-C=N-), 1723 (-O-CO-), 3299 (-NH-), 3400-3450 (-OH), ^{1}H NMR ($CDCl_3$) (δ ppm), 4.55 (s, 2H, -CH_2-), 7.11-7.50 (m, 9H, ArH, including 1H of C_5' of thiazole and 1H of -NH-), 8.45 (s, 1H, C_4 of coumarin and 10.0 (s, 1H, -H phenolic, D_2O exchangeable); Mass (m/z) 350 (M^+, 245 (100).

3-(2-(1,3-Benzoxazin-3-yl)-4-thiazolyl)coumarin (3):

Compound 2 (0.002 mol) and formalin (37%, 1 ml) were refluxed in ethanol (15 ml) for 5 hours. The residue obtained after pouring the reaction mixture into cold water was filtered, wash with water, dried and crystallised from appropriate solvent to give 3 in 60-70% yields.

3a : m.p. 166-168°C, yield, 70%, IR (ν_{max}, cm^{-1}); 1586 (-C=N-), 731 (-O-C=O), ^1H NMR (DMSO-d_6) δ (ppm) 3.68 (s, 2H, -NCH_2-), 4.90 (s, 2H, -N-CH_2-O), 6.8-7.7 (m, 8H, aromatic), 7.8 (s, 1H, C_5 of thiazole) and 8.50 (s, 1H, C_4 of coumarin); Mass (m/z) 362 (M^+), 78 (100%).

8h : m.p. 160-162°C, yield 66%, IR (ν_{max} cm^{-1}), 1586 (-C=N-), 1731 (-O-CO-), ^1H NMR ($CDCl_3$) (δ ppm), 3.48 (s, 2H, -N-CH_2-), 4.81 (s, 2H, -N-CH_2-O-), 6.80-7.70 (m, 7H, aromatic), 7.85 (s, 1H, C_5' of thiazole) and 8.40 (s, 1H, C_4 of coumarin).

Acknowledgement:

The authors are thankful to RSIC, CDRI (Lucknow) for spectral data.

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Received on June 11, 2004.