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SYNTHESIS OF 3-(2-MERCAPTO-4-THIAZOLYL)-2H-1- BENZOPYRAN-2-ONE AND ITS DERIVATIVES

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Treatment of 3-(2-bromoacetyl)coumarins with ammonium dithiocarbamate provides 3-(2-mercapto-4-thiazolyl)-2H-1-benzopyran-2-one (II) but not 4-hydroxy-4-(3-coumarinyl)thiazolidine-2-thione (I). II undergoes smooth condensation with alkyl, aralkyl, phenacyl and acid halides to give corresponding thioethers and thioesters (III) respectively. The structures of the newly synthesized compounds were established on the basis of spectral data (IR, PMR and MS).

Keywords: Mercaptothiazole; mercaptothiazolyl coumarin and ammonium dithiocarbamate

INTRODUCTION

Benzopyran-2-ones exhibit significant biological activities¹. Coumarins bearing heterocyclic moiety at the 3rd position are spasmolytic, uricosuric² and CNS active agents³. Further thiazole⁴ and also coumarin derivatives with heterocyclic system at the 3rd position exhibit promising biological activities⁵. In view of this and in continuation of our earlier work on the synthesis of heterocyclic systems from coumarin derivatives⁶⁻⁹, we report here the synthesis of new heterocyclic mercaptothiazolyl coumarins making use of 3-acetyl coumarins.

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RESULTS AND DISCUSSION

Generally 4-thiazoline-2-thiones are synthesized by the reaction of ammonium dithiocarbamate with α -haloaldehydes or ketones, when the reaction is carried out for a short time with cooling the intermediates produced are called dithiocarbamates or dithiourethanes^{10,11}. These compounds undergo cyclisation readily on standing or on heating to yield 4-thiazoline-2-thiones. The various dithiocarbamates have been generally prepared by the reaction of ammonium dithiocarbamate with α -halogeno compounds^{12,13}.

Reaction of 3-(2-bromoacetyl)coumarin with ammonium dithiocarbamate in dry ethanol afforded 3-(2-mercapto-4-thiazolyl)-2H-1-benzopyran-2-one (II) and not 4-hydroxy-4-(3-coumarinyl)thiazolidine-2-thione (I). Attempts have been made to isolate the I as an intermediate but we did not meet with success, even when the reaction is carried out in cold condition using 3-(2-bromoacetyl)coumarin and ammonium dithiocarbamate. Condensation of II with various alkyl, aralkyl, phenacyl and acid halides resulted in the formation of thioethers and thioesters respectively.

All the 3-(2-mercapto-4-thiazolyl) coumarins displayed strong absorption bands at 2700 (weak, SH)¹⁴, 1283(C=S), 1608 (C=N) and 1723 cm^{-1} (lactone -C=O).

The ^1H -NMR spectrum of the II exhibited a characteristic singlet for the C₄-of coumarin proton at δ 8.7 and thiol proton at 13.2 respectively. The remaining protons were observed in the expected regions.

Reaction of II with different alkyl, aralkyl, phenacyl and acid halides in a mixture of dry alcohol and DMF under anhydrous conditions yielded the corresponding thioethers and thioesters respectively.

EXPERIMENTS

All melting points were determined in open capillary tubes using a sulfuric acid bath and are uncorrected. IR spectra (ν_{max} cm^{-1}) were recorded on Perkin-Elmer spectrophotometer. The ^1H -NMR spectra were recorded on a varian 60 and 300 MHz respectively and the chemical shifts were recorded in δ ppm using TMS as an internal standard. The mass spectra were scanned on a Jeol-JMS-300 spectrometer at 70 eV.


TABLE I Analytical data of compounds II and III

Compd. ^a	R	m.p. ^b (°C)	Formula (m.w.)	Calc. (Found) %	
				N	S
II	H	238–40	C ₁₂ H ₇ NO ₂ S ₂ (261)	5.36 (5.32)	24.52 (24.51)
IIIa	CH ₃	292–94	C ₁₃ H ₉ NO ₂ S ₂ (275)	5.09 (5.00)	23.27 (23.25)
IIIb	-CH ₂ COCH ₃	152–54	C ₁₅ H ₁₁ NO ₃ S ₂ (317)	4.47 (4.42)	20.19 (20.00)
IIIc	-CH ₂ COOH	240–42	C ₁₄ H ₉ NO ₄ S ₂ (319)	4.39 (4.36)	20.00 (20.06)
IIId	-COCH ₂ Cl	270–72	C ₁₄ H ₈ NO ₃ S ₂ Cl (337)	4.15 (4.10)	18.99 (18.94)
IIIe	-CH ₂ COC ₆ H ₅	190–92	C ₂₀ H ₁₃ NO ₃ S ₂ (379)	3.69 (3.65)	16.88 (16.85)
IIIf	-CH ₂ COC ₆ H ₄ -p-Cl	> 300 (decomp.)	C ₂₀ H ₁₂ NO ₃ S ₂ Cl (413)	3.39 (3.36)	15.50 (15.43)
IIIg	-CH ₂ -CH=CH ₂	79–81	C ₁₅ H ₁₁ NO ₂ S ₂ (301)	4.65 (4.63)	21.26 (21.22)
IIIh	-COC ₆ H ₅	180–82	C ₁₉ H ₁₁ NO ₃ S ₂ (365)	3.84 (3.81)	17.53 (17.50)
IIIi	-CH ₂ C ₆ H ₅	220–22	C ₁₉ H ₁₃ NO ₂ S ₂ (351)	3.99 (3.96)	18.23 (18.20)
IIIj	-C(CH ₃) ₃	230–32	C ₁₆ H ₁₅ NO ₂ S ₂ (317)	4.42 (4.40)	20.18 (20.15)
IIIk	-COCH ₃	210–12	C ₁₄ H ₉ NO ₃ S ₂ (307)	4.62 (4.60)	21.12 (20.10)
IIIl	-COCH ₂ -CH ₃	200–202	C ₁₅ H ₁₁ NO ₃ S ₂ (317)	4.41 (4.38)	20.18 (20.15)

a. All the compounds were recrystallized from aqueous dimethyl formamide

b. All the compounds were obtained in 60–70% yield while II in 70%

TABLE II

IR (ν_{\max} cm^{-1})		SH	$^1\text{H-NMR}$ (δ ppm) ^a	Mass spectrum	
C=N-	C=S				
600	1180 1723	2700	7.1–7.9 (m,4H,Ar-H), 8.15 (s, 1H, C5 H of thiazole), 8.7 (s, 1H, C4 of coumarin), 13.2 (s, 1H, SH, disappeared on shaking with D ₂ O).	57(25),102(30), 145(20) 149(45), 239(98) 261(100%)	
606	–	1721	–	3.9(d, CH ₂ of allyl), 5.2–5.4 (m,2H, =CH ₂ , of allyl), 5.9–6.1 (m,1H, =CH), 7.2–7.4 & 7.5–7.8 (m,4H,Ar-H), 8.4(s,1H,thiazole), 8.7(s,1H,C4 of coumarin)	41(48), 57(40), 102(45), 145(45), 157(45), 172(50) 173(10), 174(35), 268(25) 286(100),300(10) and 301(55)
606	–	1720	–	2.4(s,3H), 4.1(s,2H, -CH ₂ -), 7.2–7.4 & 7.5–7.7 (m,4H,Ar-H), 8.4(s,1H,thiazole), 8.6(s,1H, C ₄ of coumarin)	142(17.4), 145(31.8), 158(21.7), 171(23.1), 174(23.1), 202(22.1), 242(28.8), 274(27.5) 275(98.8), 276(11.6), and 317(40.9).
–	–	–	–	4.69(s,2H,CH ₂), 7.3–7.6l(m,9H,Ar-H), 8.3(s,1H, of C5 of thiazole), 8.35 (s, 1H,C4 of coumarin).	–
–	–	–	–	4.49(s,2H,benzylic), 7.10–7.35(m, 9H,Ar-H), 8.35(s,1H, C5 of thiazole) and 8.71(s, 1H, C4 of coumarin)	–

nd II is in CDCl₃ + DMSO-d₆, IIlb and IIle in CDCl₃ while compound IIlg in DMSO-d₆ and IIli in CCl₄ + CDCl₃.

3-(2-Mercapto-4-thiazolyl)-2H-1-benzopyran-2-one (II)

A mixture of ammonium dithiocarbamate (0.01 mol) and 3-(2-bromoacetyl)coumarin (0.01 mol) in anhydrous ethanol (20 ml) was refluxed for 1 hr. The reaction mixture was cooled to room temperature. The solid obtained was filtered, washed with water and crystallized from aqueous dimethyl formamide.

3-(2-Methyl mercapto-4-thiazolyl)-2H-1-benzopyran-2-one (IIIa)

To II (0.01 mol) suspended in 10% NaOH (20 ml) at 0°C, dimethyl sulphate was added dropwise with constant shaking. The temperature was kept at 0°C and stirring was continued for another 10 minutes, during which the methylated product separated out. It was filtered and recrystallized from alcohol or from a aqueous dimethylformamide.

Reaction of II with alkyl, aralkyl, phenacyl and acid halides (III)***General Procedure***

Compound II (0.01 mol) was dissolved in a mixture of dimethyl formamide (20 ml) and anhydrous ethanol (20 ml) and appropriate alkyl, aralkyl, phenacyl or acid halide (0.01 mol) was added. The reaction mixture was refluxed for 3–4 hours at 80–90°C, then cooled, the solid separated was filtered, dried and recrystallized from a suitable solvent to give the corresponding thioethers or thioesters.

3-(2-Acetyl mercapto-4-thiazolyl)-2H-1-benzopyran-2-one (IIIk)

To a chilled solution of II (0.01 mol) in pyridine (20 ml) was added acetyl chloride (0.01 mol) with continuous shaking and the reaction mixture was refluxed for 4 hours, then cooled and poured over crushed ice. The solid separated was filtered and recrystallized.

3-(2-Carboxy methyl mercapto-4-thiazolyl)-2H-1-benzopyran-2-one (IIIc)

Equimolar quantities of II (0.01 mol) and chloroacetic acid (0.01 mol) were heated in Et-OH with few ml of 2N aqueous KOH solution on a

water-bath for 2 hours. The reaction mixture was cooled and poured over crushed ice. The solid obtained was filtered and recrystallized.

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