

A FACILE SYNTHESIS OF SOME NEW 3-(2-HYDROXY-4-THIAZOLYL) COUMARINS AND THEIR DERIVATIVES

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Abstract: Treatment of 3-(2-bromoacetyl)coumarins with potassium thiocyanate provides 3-(2-thiocyanatoacetyl)coumarins which on treatment with methanolic.HCl gives 3-(2-hydroxy-4-thiazolyl)-2H-1-benzopyran-2-ones (2) but not oxathiole derivative (4a) or 3-(2-chloro-4-thiazolyl)coumarins (4b). 2 undergoes smooth condensation with alkyl, aralkyl halides to give corresponding ethers. The structure of newly synthesized compounds were established on the basis of spectral data (IR, PMR and MS).

Introduction

Benzopyran-2-ones exhibit significant biological activities¹. Coumarins bearing a heterocyclic moiety at 3rd position are spasmolytic, uricosuric² and CNS active agents³. Further thiazole⁴ and also coumarin derivatives its heterocyclic system at 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 hydroxy thiazolyl coumarins making use of 3-acetyl coumarins.

Experimental

All melting points were determined by POLMAN-MP apparatus (Model No. MP-96). IR spectra (ν_{\max} cm⁻¹) were recorded on Perkin-Elmer spectrophotometer. The ¹H-NMR Spectra was recorded on 300 MHz instrument and the chemical shifts were recorded in δ ppm using TMS as an internal standard. The mass spectra were scanned on Perkin-Elmer SCIEX API-2000 instrument.

3-(2-thiocyanatoacetyl)-2H-1-benzopyran-2-ones (1a-d)

A mixture of 3-(2-bromoacetyl) coumarin (0.01 mol) and potassium thiocyanate (0.01 mol) in anhydrous ethanol was refluxed for 4 hrs. The reaction mixture was cooled to room temperature and filtered. The solid thus obtained was washed with water, dried and recrystallised from toluene.

3-(2-hydroxy-4-thiazolyl)-2H-1-benzopyran-2-ones (2a-d)

1a (0.01 mol) was suspended in 20 ml of methanolic-HCl (dissolve 0.6 g to 0.8 g of HCl gas in 20 ml methanol). To the above suspension 0.2 to 0.3 ml of water was added and refluxed for 4 to 6 hrs by monitoring the TLC (mobile phase Ethylacetate:Hexane in 1:1 ratio). The reaction mixture was cooled to room temperature, filtered, washed with hot toluene and recrystallised from excess methanol.

Reaction of 2 with alkyl and aralkyl halides to give 3

General Procedure for Preparing 3a-l, 7a-c

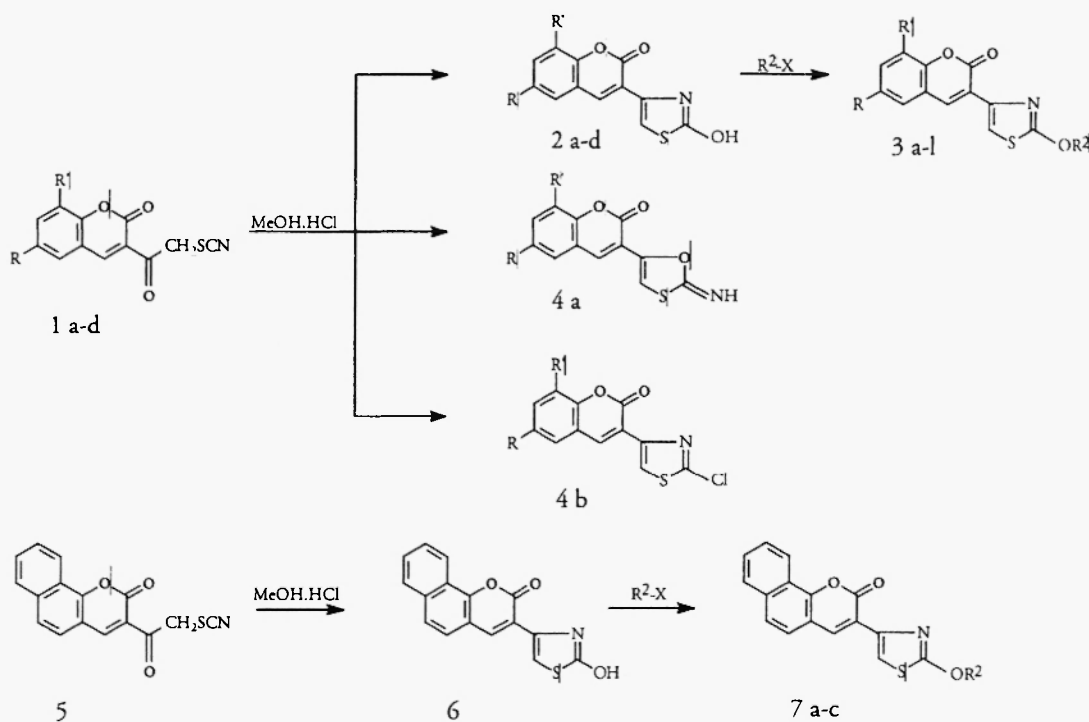
Compound 2 was suspended in dry Acetone (20ml), to this potassium carbonate (0.01 mol) and appropriate alkyl, aralkyl halide was added at 20-25 °C and the mixture was stirred at ambient temperature for 4 – 5hrs, then cooled to 5 °C. The solid was filtered, washed with chilled water, dried and recrystallised to give the corresponding ethers 3a-l and 7a-c.

3-(2-O-methyl-4-thiazolyl)-2H-1-benzopyran-2-one (3a)

To chilled suspension of 2a (0.01 mol) and potassium carbonate (0.01 mol) in anhydrous acetone (20 ml) was added methyl iodide (0.012 mol) at 15-20 °C. The reaction mixture was stirred at 20-25 °C for 5 hrs, diluted with 100 ml water and extracted with 50 ml Ethyl acetate. Solvent was evaporated to get the residue and the product was isolated from chilled methanol at 0 °C.

3-[2-O-[(2'-cyanobiphenyl-4-yl)methyl]-4-thiazolyl]-2H-1-benzopyran-2-one (3c)

Compound 2 (0.01 mol) was dissolved in dry acetone (20 ml). To this powdered potassium carbonate (0.01 mol) and 2'-cyano-4-bromomethyl biphenyl (0.01 mol) was added and the reaction mixture was stirred at 20-25 °C for 5 hrs. Cooled to 10 °C and the reaction mixture was filtered, dried and recrystallized from acetone.



Scheme 1: Synthetic sequence for preparing 2a-d, 3a-l, 6 and 7a-c compounds

Biological Essay

All of the compounds were evaluated in vitro for anti-tuberculosis activity against mycobacterium tuberculosis of the U.S.National Institute of Health, NAID division. From eleven samples tested, no compound displayed significant inhibition effects in the primary screening (mic <6.25 µg/ml) against m.tuberculosis strain 37 RV in BACTEC 12 B medium using BACTEC 460 radiometric system with rifampin as reference substance (Table 2). Compounds demonstrating at least 90% inhibition in the primary screening were re-tested in order to determine the actual minimum inhibitory concentration (mic) against m.tuberculosis. This indicates that none of the compounds exhibited noteworthy activity.

Table 1: Analytical data of compounds 2a-d, 3a-d, 6 and 7 a-c

Compd.	R	R ¹	R ²	Recrystallization Solvent	m.p* (°C)	Formula (M.W)	Calc. (Found) %	
							N	S
2a	H	H	H	A	290-92	C ₁₂ H ₇ NO ₃ S (245)	5.71 (5.68)	13.06 (13.10)
2b	Br	H	H	A	296-98	C ₁₂ H ₆ BrNO ₃ S (324)	4.32 (4.29)	9.87 (9.82)
2c	Cl	H	H	A	298-300	C ₁₂ H ₆ ClNO ₃ S (279.5)	5.00 (4.96)	11.44 (11.48)
2d	Br	Br	H	A	294-96	C ₁₂ H ₅ Br ₂ NO ₃ S (403)	3.49 (3.46)	7.94 (7.9)
6	7,8-benzo		H	A	>300	C ₁₆ H ₉ NO ₃ S (309)	4.74 (4.70)	10.84 (10.80)
3a	H	H	-CH ₃	B+A	265-67	C ₁₃ H ₉ NO ₃ S (259)	5.40 (5.36)	12.35 (12.30)
3b	H	H	-CH ₂ CH ₃	C+A	253-55	C ₁₄ H ₁₁ NO ₃ S (273)	5.12 (5.14)	11.72 (11.69)
3c	H	H	-CH ₂ .C ₆ H ₄ .C ₆ H ₄ .CN	D	240-42	C ₂₆ H ₁₆ N ₂ O ₃ S (436)	3.21 (3.20)	7.33 (7.36)
3d	Br	H	-CH ₃	B+A	268-70	C ₁₃ H ₈ BrNO ₃ S (338)	4.14 (4.10)	9.46 (9.42)
3e	Br	H	-CH ₂ CH ₃	C+A	138-40	C ₁₄ H ₁₀ BrNO ₃ S (352)	3.97 (3.92)	9.09 (9.06)
3f	Br	H	-CH ₂ .C ₆ H ₄ .C ₆ H ₄ .CN	D	223-25	C ₂₆ H ₁₅ BrN ₂ O ₃ S (515)	2.71 (2.69)	6.21 (6.18)
3g	Cl	H	-CH ₃	B+A	269-70	C ₁₃ H ₈ ClNO ₃ S (293.5)	4.77 (4.74)	10.90 (10.87)
3h	Cl	H	-CH ₂ CH ₃	C+A	138-40	C ₁₄ H ₁₀ ClNO ₃ S (307.5)	4.55 (4.53)	10.40 (10.37)
3i	Cl	H	-CH ₂ .C ₆ H ₄ .C ₆ H ₄ .CN	D	236-38	C ₂₆ H ₁₅ ClN ₂ O ₃ S (470.5)	2.96 (2.93)	6.8 (6.4)
3j	Br	Br	-CH ₃	B+A	235-37	C ₁₂ H ₅ Br ₂ NO ₃ S (403)	3.47 (3.44)	7.94 (7.92)
3k	Br	Br	-CH ₂ CH ₃	C+A	140-42	C ₁₄ H ₉ Br ₂ NO ₃ S (417)	3.35 (3.31)	7.67 (7.63)
3l	Br	Br	-CH ₂ .C ₆ H ₄ .C ₆ H ₄ .CN	D	152-54	C ₂₆ H ₁₄ Br ₂ N ₂ O ₃ S (594)	2.35 (2.32)	5.38 (5.36)
7a	-	-	-CH ₃	B+A	>300	C ₁₇ H ₁₁ NO ₃ S (309)	4.53 (4.50)	10.35 (10.32)
7b	-	-	-CH ₂ CH ₃	C+A	185-87	C ₁₈ H ₁₃ NO ₃ S (323)	4.33 (4.30)	9.90 (9.86)
7c	-	-	-CH ₂ .C ₆ H ₄ .C ₆ H ₄ .CN	D	150-52	C ₃₀ H ₁₈ N ₂ O ₃ S (486)	2.88 (2.82)	6.58 (6.53)

Note: A- Methanol; B-Isopropylether; C-Ethylacetate; D-Acetone;

* All the compounds were obtained in 60-70 % yield while 3c, 3f, 3i, 3m and 6 in 75-80 %

Table 2 Anti-tubercular activity of compounds

Compound	Assay	MIC (µg/ml)	% Inh	Activity
2a	Alamar	>6.25	0	-
3e	Alamar	>6.25	0	-
3f	Alamar	>6.25	0	-
3h	Alamar	>6.25	0	-
3i	Alamar	>6.25	0	-
3j	Alamar	>6.25	7	-
3k	Alamar	>6.25	7	-
3l	Alamar	>6.25	7	-
7a	Alamar	>6.25	7	-
7b	Alamar	>6.25	7	-
7c	Alamar	>6.25	7	-

Table 3

Compd.	IR (ν_{\max} cm^{-1})		OH	$^1\text{H-NMR}$ (δ ppm) ^a	Mass spectrum
	-C=N-	-C=O			
2a	1647	1736	3145	7.31 (s, 1H, C ₂ of thiazole), 7.63-7.96 (m, 4H, Ar-H), 8.35 (s, 1H, C ₄ of coumarin), 11.73 (s, 1H, OH at C ₂ of thiazole, disappeared on shaking with D ₂ O)	128 (5), 194 (50), 232 (10), 245 (100%)
2b	1651	1728	3151	7.32 (s, 1H, C ₂ of thiazole), 7.32-7.84 (m, 3H, Ar-H), 8.25 (s, 1H, C ₄ of coumarin), 11.79 (s, 1H, OH at C ₂ of thiazole)	121 (15), 148 (20), 241 (10), 323 (92), 325 (100%)
2c	1678	1734	3161	7.32-7.7 (m, 3H, Ar-H), 8.254 (s, 1H, C ₄ of Coumarin), 11.794 (s, 1H, OH)	142 (50), 277 (100%), 279 (55)
2d	1643	1720	3147	7.35 (s, 1H, C ₂ of thiazole), 7.83 (d, 1H, Ar-H), 8.17 (d, 2H, Ar-H), 11.82 (s, 1H, OH)	-
2e	1666	1723	3147	7.46 (s, 1H, C ₂ of thiazole), 7.58-8.226 (m, 5H, Ar-H), 8.63 (d, 1H, Ar-H), 9.1 (s, 1H, C ₄ of Coumarin), 11.93 (s, 1H, OH)	131 (100%), 148 (20), 207 (35), 220 (30), 295 (25), 309 (20)
3a	-	-	-	3.16 (s, 3H, -OCH ₃), 6.70 (s, 1H, C ₅ thiazole), 7.41-7.83 (m, 4H, Ar-H), 8.30 (s, 1H, C ₄ of coumarin)	126 (5), 170 (5), 200 (5), 231 (5), 259 (100%), 281 (50 Na adduct)
3b	-	-	-	1.42 (t, 3H, -CH ₃), 4.53 (q, 2H, -CH ₂), 7.37-7.9 (m, 5H, Ar-H including 1H at C ₅ of thiazole), 8.63 (s, 1H, C ₄ of coumarin)	131 (10), 144 (20), 245 (30), 273 (100%)
3c	-	-	-	5.68 (s, 2H, -CH ₂ -biphenyl), 7.48-7.90 (m, 13H, Ar-H including 1H at C ₅ of thiazole), 8.73 (s, 1H, C ₄ of coumarin)	131 (100%), 148 (70), 191 (70), 283 (60), 312 (100%), 390 (45), 436 (60), 458 (20 Na adduct)
3d	-	-	-	3.16 (s, 3H, -OCH ₃), 6.7 (s, 1H, thiazole), 7.47 (m, 2H, Ar-H), 7.87 (d, 1H, C ₅ of coumarin), 8.23 (s, 1H, C ₄ of coumarin)	148 (10), 336 (95), 338 (100%)
3e	-	-	-	1.42 (t, 3H, -CH ₃), 4.53 (q, 2H, -OCH ₂ -), 7.40-8.18 (m, 4H, Ar-H), 8.62 (s, 1H, C ₄ of coumarin)	-
3f	-	-	-	5.62 (s, 2H, -OCH ₂ -), 7.25-7.97 (m, 12 H, Ar-H), 8.52 (s, 1H, C ₄ of coumarin)	-
3g	-	-	-	3.15 (s, 3H, -OCH ₃), 6.70 (s, 1H, thiazole), 7.56-8.23 (m, 3H, Ar-H), 8.50 (s, 1H, C ₄ of coumarin)	-

Table 3Con d.

Compd.	IR (ν_{\max} cm ⁻¹)		OH	¹ H NMR (δ ppm) ^a	Mass spectrum
	C=N	C=O			
3h	-	-	-	1.51(t, 3H, -CH ₃), 4.54 (q, 2H, -CH ₂), 7.27-7.6 (m, 3H, Ar-H), 7.92 (s, 1H, C ₅ of thiazole), 8.49 (s, 1H, C ₄ of coumarin)	214 (10), 279 (25), 281 (10), 307 (55), 309 (25), 329 (100% Na adduct), 331 (50)
3i	-	-	-	5.63(s, 2H, -OCH ₂), 7.31-7.98 (m, 13H, Ar-H including C ₅ of thiazole), 8.73 (s, 1H, C ₄ of coumarin)	-
3j	-	-	-	3.17 (s, 3H, -OCH ₃), 6.71 (s, 1H of C ₅ thiazole), 8.08-8.24 (m, 3H, Ar-H including C ₄ of coumarin)	-
3k	-	-	-	1.5(t, 3H, -CH ₃), 4.53 (q, 2H-OCH ₂ -), 7.27 (s, 1H, C ₅ of thiazole) 7.69-7.91 (m, 3H, Ar-H), 8.42 (s, 1H, C ₄ of coumarin)	-
3l	-	-	-	5.61(s, 2H, -OCH ₂), 7.27 (s, 1H, C ₅ of thiazole), 7.48-7.99 (m, 10H, Ar-H), 8.42 (s, 1H, C-4 of coumarin)	-
7a	-	-	-	3.19 (s, 3H, -OCH ₃), 6.77 (s, 1H, C ₅ of thiazole), 7.62-8.67 (m, 6H, Ar-H), and 9.107 (s, 1H, C ₄ of coumarin)	148 (10), 174 (8), 279 (5), 301 (8), 309 (100%), 331 (30 Na adduct)
7b	-	-	-	1.54 (t, 3H, -OCH ₂), 4.64 (q, 2H, OCH ₂), 7.48-7.99 (m, 7H, Ar-H), 8.42 (s, 1H, C ₄ of coumarin)	148 (5), 199 (5), 215 (5), 252 (7), 295 (20), 323 (100%), 345 (30 Na adduct)
7c	-	-	-	5.7 (s, 2H, -OCH ₂), 7.48-8.03 (m, 14H, Ar-H including C ₅ of thiazole), 8.45 (d, 1H, Ar-H), 9.40 (s, 1H, C ₄ of coumarin)	-

a. Compound 2, 3a-e, 3j and 7a in DMSO-d₆ while 3f, 3g, 3h, 3i, 3k, 3l, 7b and 7c in CDCl₃.

Results and Discussion

Reaction of 3-(2-bromoacetyl)coumarins¹⁰ with potassium thiocyanate in dry ethanol afforded 3-(2-thiocyanatoacetyl)coumarins. These on reaction with methanolic hydrochloric acid (Scheme 1) resulted in the formation of cyclized products namely 3-(2-hydroxy-4-thiazolyl)coumarins (2) and not 3-(2-imino-1,3-oxathioly)coumarins(4a).

It has been reported in the literature that reaction between 3-(2-thiocyanatoacetyl)coumarins and HCl resulted in the formation of 3-(2-chloro-4-thiazolyl)coumarins¹¹. In contrast to this report surprisingly we have noticed that the reaction between 3-(2-cyanatoacetyl)coumarins with methanolic HCl gave the 3-(2-hydroxy-4-thiazolyl)coumarins instead of expected 3-(2-chloro-4-thiazolyl)coumarins. The present method of preparation of title compounds is a modified Hantzsch thiazole synthesis. It is a single step, less time consuming, involves simple work-up procedure is of general applicability and yields of the products are high.

This is a first unexpected report of the formation of 2-hydroxy thiazoles in the Hantzsch thiazole synthesis starting from α -thiocyanatoketones. This general method may be applied to the synthesis of other hydroxy thiazoles. Condensation of 2 with various alkyl, aralkyl halides resulted in the formation ethers (3 and 7).

All the 3-(2-hydroxy-4-thiazolyl)coumarins displayed strong absorption bands at 3145-3161 (OH) and 1723-1734 cm^{-1} (lactone $\text{C}=\text{O}$). The ^1H NMR spectrum of the 2 exhibited a characteristic singlet for the C_4 of coumarin proton at δ 8.25 and OH proton of C_2 of thiazole at δ 11.79. The remaining protons were observed in the expected region.

Conclusions

In summary, we have prepared 3-(2-hydroxy-4-thiazolyl)coumarins (2) in a single step starting from 3-(2-thiocyanatoacetyl)coumarins (1) in high yields. The compounds were subsequently converted into their basic ethers (3). The compounds prepared have been subjected for their anti tubercular activity. None of the compounds prepared have shown antitubercular activity.

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