REACTIONS WITH COUMARINS: SYNTHESIS OF SEVERAL NEW ANNELATED PYRIDINE AND PYRROLYLCOUMARIN DERIVATIVES

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Abstract - Benzopyronopyridine, pyrazolo[3,4-d]-pyridine, isoxazolo[5,4-b]-pyridine, pyrido[2,3-d]pyrimidine and pyrrolylcoumarin derivatives were synthesized from 3-acetylcoumarin and its derivatives with different reagents.

INTRODUCTION

Coumarin and its annelated derivatives are reported to possess significant antibacterial,[1] coronary dilatory[2] and hypothermal[3] activities. Therefore, it became of interest to synthesize new derivatives of these systems of expected biological activities. The use of the readily obtainable 3-acetylcoumarin (1) seemed to be a logic and easy route for the synthesis. The reactions of 1 with different reagents resulted in the synthesis of several annelated coumarin derivatives which are needed for a biological activity program.

DISCUSSION

Thus, it has been found that 1 reacted with malononitrile (2a) in ethanol in the presence of catalytic amount of triethylamine to afford a product of molecular formula $C_{14}H_{10}N_2O_3$ corresponding to the addition of one molecule of 1 to one molecule of 2a. The reaction product

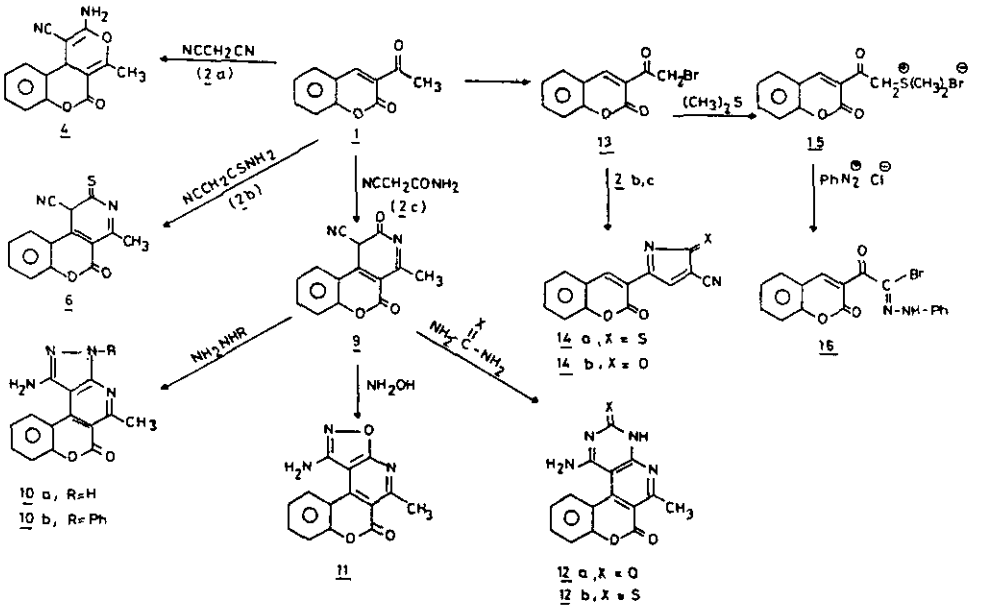
could, however, be formulated as the pyranocoumarin derivative (4) on the basis of spectral data. The ir (cm^{-1}, KBr) spectrum of 4 showed absorption bands for NH_2 (3400,3350) CN (2220), and C=O (1680) groups while its ^{1}H-nmr spectrum ($CDCl_3$) revealed signals (δ ppm) 2.8 (s, 3H, CH_3), 4.8 (s, 1H pyran H-4), 7.4-7.9 (m, 4H, ArH's) and 9.8 (br s, 2H, NH_2).

Similarly, 1 reacted with cyanothioacetamide (2b) to yield a product resulted from the addition of one molecule of 1 to another moelcule of 2b followed by the loss of the elements of water and two hydrogens. The ir (cm^{-1}, KBr) spectrum of the reaction product showed absorption bands corresponding to the presence of CN (2220), CO (1680), C=N (1620) and C=S (1540) groups while its ^{1}H-nmr (DMSO-d_6) spectrum revealed signals for CH_3 (3.0, s), dihydropyridine-thione H-3 (3.9, s) in addition to the signals of the aromatic protons (7.0-7.8, m). Based on the above evidences other formulas were ruled out and the reaction product could be formulated as the benzopyrano[3,4-c]pyridine derivative (6) (cf. Scheme 1).

In a similar manner, compound (1) reacted with cyanoacetamide (2c) to give a compound corresponding to the addition product of one molecule of 1 to one molecule of 2c and the loss of water and a molecule of hydrogen. The benzopyrano[3,4-c]pyridine structure could be assigned to the reaction product (9) on the bases of correct elemental analysis and spectral data. Thus, the ir (cm^{-1}, KBr) spectrum of 9 showed absorption bands related to the presence of CN (2220), CO (1690), and C=N (1630) groups. The ^{1}H-nmr (DMSO-d_6) (δ ppm) spectrum revealed signals of CH_3 (2.3, s), pyridine H-3 (3.8, s) in addition to the aromatic protons (7.5-8.1, m, 4H). The signal at 3.8 (δ ppm) corresponded to one proton indicating that the reaction product suffered autoxidation under the applied reaction conditions. This fact has been observed previously for similar ring systems,[4,5] (cf. Scheme 1 and Table 1).

Compound (9) was taken as the key compound for other heterocyclic derivatives and its synthetic potential was demonstrated via a series of reactions. Thus compound (9) reacted with hyrazine hydrate in ethanol to afford the corresponding pyrazolo[3,4-b]pyridine derivative (10a) and similarly the reaction of phenylhydrazine resulted in the formation of the pyrazolo[3,4-b]-pyridine derivative (10). (cf. Tables 1 and 2) Moreover, hydroxylamine reacted also with 9 and the reaction product could be formulated as the isoxazolo[5,4-b]pyridine derivative (11). Compound (9) reacted also with urea and with thiourea under basic conditions to offered products resulting from the addition of one molecule of 9 to one molecule of each of the ureas with the loss of one molecule of water in each case. The reaction products could then be

formulated as the pyrido[2,3-d]pyrimidine derivatives (12a,b) respectively. Thus 13[6] reacted, base catalysed, with each of cyanothioacetamide (2b) and with cyanoacetamide (2c) to yield the corresponding 3-(2'-pyrrolyl)coumarin derivatives (14a,b) respectively. The ^{1}H-nmr spectra of 14a,b did not reveal any signals for CH_2 groups in the range of 3-5 (δ ppm) indicating that



Scheme 1

reaction products suffered autoxidation under the applied reaction conditions and revealed only the multiplet of aromatic and pyrrole protons (7.5-8.1) in each case (cf. Tables 1 and 2). Compound (13) reacted with dimethyl sulfide to yield the dimethylsulfonium bromide derivative (15) which could be coupled with benzenediazonium chloride to give the corresponding hydrazidoyl bromide (16). Structures (15) and (16) were confirmed and established on the basis of correct elemental analyses and spectral data studies (cf. Tables 1 and 2).

EXPERIMENTAL

All melting points are uncorrected. Ir spectra were recorded (KBr) on Pye Unicam SP-1100 spectrophotometer. ^{1}H-Nmr spectra were recorded in $CDCl_3$ (compounds 10a,b, 12a, 15, 16) or DMSO-d_6 (compounds 12b, 14a,b) on a varian EM 390 90 MHz using TMS as an internal

reference and chemical shifts are expressed as δ ppm units. Elemental analyses were performed by the Microanalytical Center at Cairo University. 3-Bromoacetylcoumarin (**13**) was prepared according to literature procedure.[6]

Reaction of 1 with 2a-c:

Ceneral Procedure: A solution of **1** (1.88 g, 0.01 mol) and each of **2a-c** (0.01 mol) in ethanol (30 ml) containing triethylamine (0.5 ml) was heated under reflux for 4 h. The reaction products obtained after cooling were filtered off and recrystallized from the proper solvent to give **4**, **6** and **9** respectively. (cf. Table 1).

Reaction of 9 with hydrazines:

A solution of **9** (2.52 g, 0.01 mol) and each of hydrazine hydrate or phenylhydrazine (0.01 mol) in ethanol (60 ml) was heated under reflux for 3 h. The solid products obtained after concentration and cooling were filtered off and recrystallized from the proper solvent to give **10a,b** respectively (cf. Tables 1 and 2).

Reaction of 9 with hydroxylamine HCl:

A solution of **9** (2.52 g, 0.01 mol) and hydroxylamine HCl (0.07 g, 0.01 mol) in ethanol (60 ml) containing dry potassium carbonate (1 g) was heated under reflux for 3 h. The reaction product obtained after dilution with water was filtered off, then washed with water and recrystallized from the proper sovlent to give **11** (cf. Tables 1 and 2).

Table (1): Characterization data of the newly synthesised compounds.

Comp.	Colour (solvent)	mp (°C)	Yield (%)	Formula	% Analysis Calcd/Found				
					C	H	N	S	Br
4	Brown (DMF)	235	50	$C_{14}H_{10}N_2O_3$	66.1 66.4	3.9 4.2	11.0 10.8	- -	- -
6	Buff (ethanol)	160	75	$C_{14}H_8N_2O_2S$	62.7 62.4	3.0 3.3	10.4 10.6	11.9 12.1	- -
9	Yellow (ethanol/ acetone)	250	55	$C_{14}H_8N_2O_3$	66.7 66.9	3.2 3.5	11.1 11.4	- -	- -
10a	Yellow (ethanol/ acetone)	280	55	$C_{14}H_{10}N_4O_2$	63.2 63.0	3.8 4.0	21.1 20.7	- -	- -

Table (1) Contd.

Comp.	Colour (solvent)	mp (°C)	Yield (%)	Formula	% Analysis Calcd/Found				
					C	H	N	S	Br
10b	yellow (ethanol/ acetone)	270	50	$C_{20}H_{14}N_4O_2$	70.2 70.4	4.1 3.8	16.4 16.0	- -	- -
11	Brown (ethanol/ acetone)	250	50	$C_{14}H_9N_3O_3$	62.9 63.2	3.4 3.6	15.7 16.0	- -	- -
12a	Yellow (ethanol)	240	50	$C_{15}H_{10}N_4O_3$	61.2 61.0	3.4 3.6	19.0 18.8	- -	- -
12b	Yellow (ethanol)	190	50	$C_{15}H_{10}N_4O_2S$	58.1 57.8	3.2 3.0	18.1 17.9	10.3 10.1	- -
14a	Yellow (ethanol)	175	60	$C_{14}H_6N_2O_2S$	63.2 62.9	2.3 2.1	10.5 10.3	12.0 11.8	- -
14b	Pale green (ethanol)	190	50	$C_{14}H_6N_2O_3$	67.2 66.9	2.4 2.2	11.2 10.9	- -	- -
15	Pale yellow (ethanol)	150	70	$C_{13}H_{13}O_3BrS$	47.4 47.2	4.0 4.1	- -	9.7 9.9	24.3 24.1
16	Red (ethanol)	175	60	$C_{17}H_{11}N_2O_3Br$	55.0 55.2	3.0 3.1	7.5 7.4	- -	21.6 21.2

Reaction of 9 with ureas:

A solultion of **9** (2.52 g, 0.01 mol) and each of urea or thiourea (0.01 mol) in ethanol (30 ml) containing triethylamine (0.5 ml) was heated under reflux for 3 h. The solids obtained after cooling were filtered off, recrystallized and identified as **12a,b** respectively (cf. Tables 1 and 2).

Reaction of 13 with 2b,c:

A solution of **13**[6] (2.67 g, 0.01 mol) and each of **2b,c** (0.01 mol) in ethanol (30 ml) containing triethylamine (0.5 ml) was refluxed for 3 h. The solids so formed on cooling were filtered off and recrsytallized from the proper solvent to give **14a,b** respectively (cf. Tables 1 and 2).

Table 2: Ir and ^{1}H-Nmr data.

Comp.	ir (cm^{-1}) (KBr)	^{1}H-nmr (δ ppm)
10a	3400, 3350, 3330 (NH_2 and NH), 1680 (CO) and 1630 (C=N).	2.8 (s, 3H, CH_3), 7.4-8.0 (m, 4H, ArH's) and 9.3 (br s, 3H, NH and NH_2).
10b	3420, 3350 (NH_2), 1690 (CO) and 1630 (C=N).	2.8 (s, 3H, CH_3), 7.5-8.1 (m, 9H, ArH's) and 9.6 (br s, 2H, NH_2).
12a	3400, 3380, 3300 (NH_2) and (NH), 1690, 1670 (two CO) and 1630 (C=N).	2.9 (s, 3H, CH_3), 7.6-8.0 (m, 4H, ArH's) and 9.7 (br s, 3H, NH_2 and NH).
12b	3420, 3350, 3320 (NH_2 and NH), 1680 (CO), 1630 (C=N) and 1520 (C=S).	2.9 (s, 3H, CH_3), 7.6-7.9 (m, 4H, ArH's) and 9.8 (br s, 3H, NH_2 and NH).
14a	2220 (CN), 1680 (CO), 1620 (C=N) and 1540 (C=S).	7.6-8.0 (m, 6H, ArH).
14b	2220 (CN), 1690, 1670 (two CO) and 1630 (C=N).	7.6-8.0 (m, 6H, ArH).
15	1710 (CO) and 1680 (CO).	2.1 (s, 6H, two CH_3), 4.0 (s, 2H, CH_2) and 7.4-7.9 (m, 5H, ArH).
16	3300 (NH), 1690 (CO), 1670 (CO) and 1620 (C=N).	7.6-8.0 (m, 10 H, ArH) and 9.6 (br s, 1H, NH).

Reaction of 13 with dimethyl sulfide:

A solution of **13** (2.67 g, 0.01 mol) in ethanol (30 ml) was treated with dimethyl sulfide (0.06 ml, 0.01 mol) and the reaction mixture was then refluxed for 30 min. The reaction mixture was cooled and ether was added whereby **15** precipitated which was filtered off, washed with little ether, then crystallized from the proper sovlent (Table 2).

Formation of 16:

A cold solution of **15** (3.29 g, 0.01 mol) in acetic acid (30 ml) containing sodium acetate (1 g) was treated with a cold solution of the corresponding diazotised aniline (1.86 g, 0.02 mol) (prepared by $NaNO_2$ (1.58 g, 0.023 mol) and 15 % HCl (11 ml)) dropwise with stirring while the temperature was kept below 5^{o}C. After complete addition (30 min) the reaction mixture

was further kept in the ice-chest for 2 h. The solid so formed was filtered off, washed with water, then recrystallized from the proper solvent to give **16** (cf. Table 2).

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Received, 17th December, 1990