Activated Nitriles in Heterocyclic Synthesis. Novel Synthesis of 5-Imino-5*H*-[1]benzopyrano[3,4-*c*]pyridine-4(3*H*)-thiones and Their Oxo Analogues

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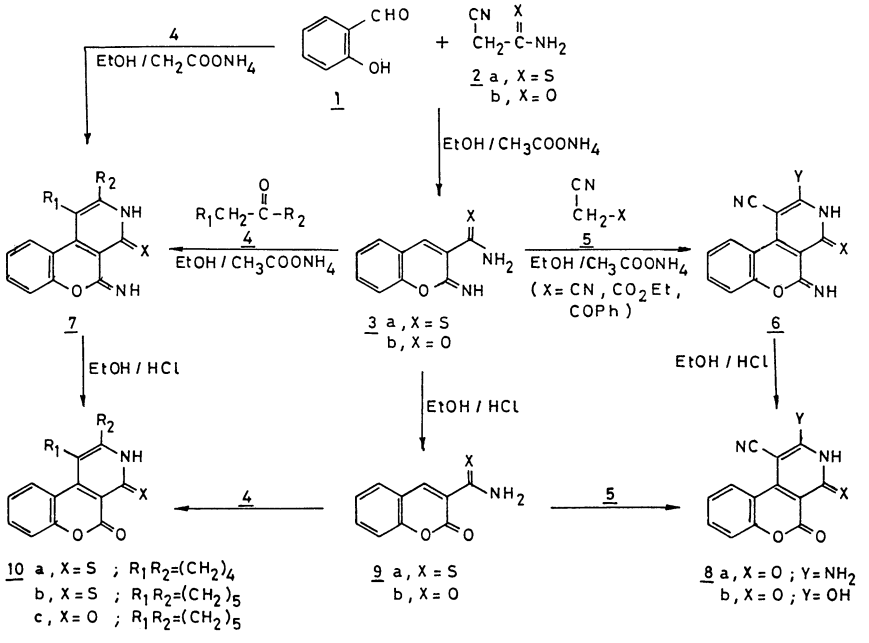
Various benzopyrano[3,4-*c*]pyridine-4(3*H*)-thione derivatives and their oxo analogues were prepared by condensation of cyanothioacetamide or cyanoacetamide and salicylaldehyde with ketones or activated nitriles in the presence of ammonium acetate.

The utilities of cyano compounds in organic synthesis are now receiving considerable interest.[1,2] As a part of our program directed for development of new simple and efficient procedures for the synthesis of fused heterocyclic nitrogen compounds utilizing readily obtainable nitriles intermediates.[3,4] We have previously reported several new approaches for the synthesis of condensed heterocycles utilizing 2-cyanomethylbenzimidazole[5] and 2-cyanomethylbenzthiazole[6] derivatives as starting material. In conjunction of this work we report a novel synthesis of benzopyranopyridines utilizing the coumarin derivative **3** as starting material. Compound **3** can be prepared by the reaction of cyanothioacetamide or cyanoacetamide with salicyladehyde in EtOH/ammonium acetate mixture at 50 °C for 10 min. Compound **3** reacted in a 1 : 1 molar ratio with acetone, acetophenone, or cyclic ketones **4c—e** in the presence of catalytic amounts of ammonium acetate in refluxing ethanol to give the 4-thioxo- or 4-oxo-5-imino-5*H*-[1]benzopyrano[3,4-*c*]-pyridine derivatives **7**. The structures of **7** could be established for the reaction products based on elemental analyses and spectral data (^{1}H NMR, IR, and MS). Compound **7** could also be prepared by the condensation of salicyladehyde, ketones **4** and cyanothioacetamide or cyanoacetamide (molar ratio 1 : 1 : 1) in the presence of ammonium acetate. Compounds **7**, when heated with hydrochloric acid in ethanol, were converted to 5-oxo derivatives **10**, which was proved to be the same as those obtained from the reaction of **9** with ketones **4**. Compound **3** reacted with malononitrile, ethyl cyanoacetate, or benzoylacetonitrile (**5a—c**) in refluxing ethanol containing catalytic amounts of ammonium acetate for 3 h to give the benzopyranopyridine derivatives **6**. When **6** are refluxed with HCl/EtOH, the 5-oxo derivative **8** was obtained.



6 a, X = S ; Y = NH_2
b, X = S ; Y = OH
c, X = S ; Y = C_6H_5
d, X = O ; Y = NH_2
e, X = O ; Y = OH

7 a, X = S ; R_1 = H ; R_2 = CH_3
b, X = O ; R_1 = H ; R_2 = CH_3
c, X = S ; R_1 = H ; R_2 = C_6H_5
d, X = O ; R_1 = H ; R_2 = C_6H_5
e, X = S ; R_1R_2 = $(CH_2)_3$
f, X = O ; R_1R_2 = $(CH_2)_3$
g, X = S ; R_1R_2 = $(CH_2)_4$
h, X = O ; R_1R_2 = $(CH_2)_4$
i, X = S ; R_1R_2 = $(CH_2)_5$
j, X = O ; R_1R_2 = $(CH_2)_5$

The formation of **6** or **7** from **3** and **5** or **3** and **4** is assumed to proceed via the addition of an active methylene group of the nitriles **5** or alkanones **4** to the double bond of **3** to give an intermediate Michael adduct. This Michael adduct then cyclizes to give an intermediate dihydropyridine, which is oxidized under the reaction conditions to yield the 5-iminobenzopyranopyridine derivatives **6** and **7**. These results indicate that the reaction of **3** with suitable active methylene compounds can be utilized as an excellent route for the synthesis of several, otherwise difficulty accessible fused coumarin derivatives. The synthesized compounds revealed promising for further chemical transformations and for biological testing.

Experimental

All melting points are uncorrected. IR spectra were obtained (KBr) on a Pye Unicam 1000 spectrophotometer and on a Shimadzu IR 200. ^{1}H NMR spectra were measured on a Varian EM 390-90 MHz in DMSO using TMS as internal standard and chemical shifts are expressed as δ/ppm. Analytical data were obtained from the analytical data unit at Cairo University.

Table 1. Compounds **3a,b**; **6a—e**; **7a—j**; **8a,b**; **9a,b**; and **10a—c**

Compound	Solvent of cryst.	Mp °C	Yield/%	Mol. formula	Found/Calcd(%) C	H	N
3a	EtOH	146	80	$C_{10}H_8N_2OS$	59.2	4.2	13.3
					58.8	3.9	13.7
3b	EtOH	178	88	$C_{10}H_8N_2O_2$	63.4	4.0	14.6
					63.8	4.3	14.9
6a	DMF	>300	77	$C_{13}H_8N_4OS$	57.8	3.4	20.6
					58.2	3.0	20.9
6b	MeOH-DMF	>300	48	$C_{13}H_7N_3O_2S$	57.7	3.0	15.4
					58.0	2.6	15.6
6c	MeOH-DMF	>300	65	$C_{19}H_{11}N_3OS$	69.0	3.6	12.5
					69.3	3.3	12.8
6d	DMF	>300	68	$C_{13}H_8N_4O_2$	62.1	3.4	21.8
					61.9	3.2	22.2
6e	EtOH-DMF	>300	70	$C_{13}H_7N_3O_3$	61.8	3.1	16.3
					61.7	2.8	16.6
7a	MeOH	270—72	55	$C_{13}H_{10}N_2OS$	64.1	3.8	11.2
					64.5	4.1	11.6
7b	MeOH	272—74	80	$C_{13}H_{10}N_2O_2$	68.7	4.4	12.0
					69.0	4.4	12.4
7c	EtOH	>300	60	$C_{18}H_{12}N_2OS$	70.8	4.2	8.9
					71.1	3.9	9.2
7d	EtOH	215	66	$C_{18}H_{12}N_2O_2$	74.8	4.4	9.5
					75.0	4.2	9.7
7e	EtOH	130	52	$C_{15}H_{12}N_2OS$	66.9	4.4	10.1
					67.2	4.5	10.4
7f	Dioxane	258	70	$C_{15}H_{12}N_2O_2$	71.0	5.0	10.8
					71.4	4.8	11.1
7g	MeOH	172	82	$C_{16}H_{14}N_2OS$	67.8	4.8	9.6
					68.1	5.0	9.9
7h	Dioxane	>300	85	$C_{16}H_{14}N_2O_2$	71.9	5.5	10.1
					72.2	5.3	10.5
7i	EtOH	135	50	$C_{17}H_{16}N_2OS$	69.1	5.4	9.2
					68.9	5.4	9.5
7j	EtOH	208—10	56	$C_{17}H_{16}N_2O_2$	73.0	5.5	9.7
					72.9	5.7	10.0
8a	DMF	292—94	40	$C_{13}H_7N_3O_3$	72.0	3.1	16.3
					61.7	2.8	16.6
8b	DMF	285—87	50	$C_{13}H_6N_2O_4$	61.1	2.7	10.7
					61.4	2.4	11.0
9a	DMF	230—32	66	$C_{10}H_7NO_2S$	58.3	3.6	6.5
					58.5	3.4	6.8
9b	DMF	258—60	70	$C_{10}H_7NO_3$	63.2	4.0	7.1
					63.5	3.7	7.4
10a	EtOH-DMF	202—04	58	$C_{16}H_{13}NO_2S$	67.5	4.8	4.6
					67.8	4.6	4.9
10b	EtOH-DMF	186	70	$C_{17}H_{15}NO_2S$	68.6	4.8	4.4
					68.7	5.1	4.7
10c	DMF	217—19	60	$C_{17}H_{15}NO_3$	72.4	5.0	4.7
					72.6	5.3	5.0

Table 2. Spectral Data for the Compounds Listed in Table 1

Compound	IR/cm^{-1} (Selected bands)	^{1}H NMR (δ/ppm)
6b	3400 (NH)	7.02—7.80 (m, 4H, C_6H_4); 8.3 (s, br, 1H, NH); 10.18 (s, br, 1H, NH); 11.9 (s, br, 1H, OH)
6c	3320, 3420 (NH)	7.2—7.90 (m, 9H, C_6H_5, C_6H_4); 8.21 (s, br, 1H, NH); 10.1 (s, br, 1H, NH)
7a	3380, 3420 (NH)	2.38 (s, 3H, CH_3); 7.12—7.7 (m, 5H, C_6H_4, pyridine H-3); 8.1 (s, br, 1H, NH); 8.32 (s, br, 1H, NH)
7c	3430 (NH)	6.68 (m, 1H, pyridin H-3); 7.2—7.7 (m, 4H, C_6H_4); 8.14 (s, br, 1H, NH); 8.25 (s, br, 1H, NH)
7d	3300, 3380 (NH)	6.75 (m, 1H, pyridine H-3); 7.1—7.65 (m, 4H, C_6H_4); 8.08 (s, br, 1H, NH); 8.2 (s, br, 1H, NH)
7h	3350, 3400 (NH)	1.6—2.0 (m, 2H, CH_2); 2.42—2.6 (m, 2H, CH_2); 2.69—2.92 (m, 2H, CH_2); 2.95—3.12 (m, 2H, CH_2); 7.1—7.8 (m, 4H, C_6H_4); 8.2 (s, br, 1H, NH); 8.9 (s, br, 1H, NH)
7j	3380, 3420 (NH)	1.68 (m, 2H, CH_2); 1.8 (m, 2H, CH_2); 1.98 (m, 2H, CH_2); 2.55 (m, 2H, CH_2); 2.86 (m, 2H, CH_2); 7.0—7.7 (m, 4H, C_6H_4); 8.0 (s, br, 1H, NH); 8.6 (s, br, 1H, NH)
10a	3450 (NH); 1690—1700 (CO)	1.7—2.1 (m, 2H, CH_2); 2.3—2.58 (m, 2H, CH_2); 2.66—2.90 (m, 2H, CH_2); 2.96—3.2 (m, 2H, CH_2); 7.0—7.67 (m, 4H, C_6H_4); 8.4 (s, br, 1H, NH)

Coumarin Derivatives 3a,b. A mixture of cyanothioacetamide or cyanoacetamide (0.01 mol), salicyladehyde (0.01 mol), and ammonium acetate (0.015 mol) in ethanol (30 ml) was heated at 50 °C for 10 min. The resulting solid product was collected by filtration and crystallized from the proper solvent (cf. Table 1).

5-Imino-5*H*-[1]benzopyrano[3,4-*c*]pyridine Derivatives 6a—e and 7a—j. A mixture of **4** or **5** (0.01 mol), coumarin **3** (0.01 mol), and ammonium acetate (0.015 mol) in ethanol (40 ml) was refluxed for 3 h. The resulting solid product was collected by filtration and crystallized from the proper solvent (cf. Table 1).

5-Oxo-5*H*-[1]benzopyrano[3,4-*c*]pyridine Derivatives 8a,b and 10a—c. A solution of **6** or **7** (0.01 mol) in ethanol (30 ml) was treated with concentrated (37.5%) hydrochloric acid (5 ml). The reaction mixture was heated under reflux for 2 h and then evaporated under reduced pressure. The remaining product was triturated with water and neutralized by addition of aqueous ammonia. The solid product was filtered off and crystallized from the appropriate solvent.

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