Synthesis of *N*-(9-Oxo-7-phenyl-9*H*-pyrano[2,3-*g*]benzothiazol-2-yl)benzamides from 6-Aminoflavone

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Synopsis. 6-Aminoflavone[1] (**1**) was treated with aroyl isothiocyanate in acetone at reflux temperature yields *N*-aroyl-*N'*-(2-phenyl-4-oxo-4*H*-[1]benzopyran-6-yl)thioureas (**2**). The products obtained on reaction of **2** with PCl_5 in $POCl_3$ medium leads to *N*-(9-oxo-7-phenyl-9*H*-pyrano[2,3-*g*]-benzothiazol-2-yl)benzamides (**4**). The structures of the compounds synthesized were established by analytical and spectral data.

A large number of thiazole derivatives have been found to exhibit pharmacological activities[2—4] and some of them are used as chemotherapautic agents.[5,6] In view of the pharmaceutical importance of thiazole derivatives it was proposed to synthesize *N*-(9-oxo-9*H*-pyrano[2,3-*g*]benzothiazol-2-yl)benzamides from 6-aminoflavone by novel methods. Flavone ring fused to thiazole ring have not been reported in literature.

6-Aminoflavone[1] (**1**) with benzoyl isothiocyanate at reflux temperature for 2 h afforded *N*-benzoyl-*N'*-(2-phenyl-4-oxo-4*H*-[1]benzopyran-6-yl)thiourea (**2a**), mp 187—190°C, M^+ 400, analyzed for $C_{23}H_{16}N_2O_3S$. The IR spectrum showed absorption at 3250 cm^{-1} (br. NH), 1665 (amide carbonyl), 1645 (benzopyrone carbonyl), and 1250 cm^{-1} (C=S). The ^1H NMR spectrum ($CDCl_3$) δ=6.80 (1H, S, C_3–H), 8.38 (1H, d, J=1.95 Hz, C_5–H), 7.22 (1H, m, C_7–H), 7.36 (1H, m, C_8–H), 12.80 (1H, s, –CO–NH), 9.10 (1H, s, –CS–NH), 7.92 (4H, m, C_2', 6′ & C_2'', 6″–H), 7.58 (6H, m C_3', 4′, 5′ & C_3'', 4″, 5″–H).

On refluxing **2a** with PCl_5 in $POCl_3$ medium at 120°C for 2 h the reaction mixture upon chromatographic purification afforded *N*-(9-oxo-7-phenyl-9*H*-pyrano[2,3-*g*]benzothiazol-2-yl)benzamide (**4a**), mp 220°C (decomposed), M^+ 398, analyzed for $C_{23}H_{14}N_2O_3S$ (Table 1). The IR spectrum showed absorptions at 3250—3000 cm^{-1} (br. NH), 1668 cm^{-1} (amide carbonyl) and 1620 cm^{-1} (Benzopyrone carbonyl). The ^1H NMR spectrum (CF_3COOD) revealed AB doublets at δ=8.02 (C_4–H, J=9.5 Hz) and 8.38 (C_5–H, J=9.5 Hz) which indicated the fusion is angular (**4a**—**d**). The C_8–H resonated at δ=7.38. The NH signal was not observed due to solvent exchange. Thus the ^1H NMR spectra ruled out the formation of linear structure (**5**).

The formation of **4a** from **2a** can be explained as follows (Scheme 1): *N*-Benzoyl-*N'*-(2-phenyl-4-oxo-4*H*-[1]benzopyran-6-yl)thiourea (**2a**) possesses both amide and thioamide functions respectively. Therefore in the reaction of **2a** with PCl_5 in $POCl_3$ medium it is reasonable to expect the nucleophilic attack on either carbonyl oxygen or on thiocarbonyl sulfur to give **7a** or **4a** respectively (path a or path b). Intramolecular nucleophilic attack of the ring nitrogen on the carbon and the heterolysis of C–O bond in **6** would result in the formation of **7a—d** (path a). Whereas similar nucleophilic attack of nitrogen at C_6 of flavone ring on electron-deficient sulfur atom which bonded to a positively charged phosphorus atom and heterolysis of S–P bond in **3** leads to thiazole ring (path b). The reaction tool place by path b which resulted in the formation of *N*-(9-oxo-7-phenyl-9*H*-pyrano[2,3-*g*]benzothiazol-2-yl)benzamide (**4a**). Compound (**7**) was not isolated in this reaction.

The superior nucleophilicity in thiocarbonyl sulfur compared to carbonyl oxygen in **2a** and the tendency for preferential formation of a five-membered ring, which are generally observed in heterocyclic structures may be responsible for the exclusive formation of **4a** from **3**.

The above two structures **7** and **4** can be distinguished by IR spectrum. In compound (**7**) C=S stretching would be found at 1250 cm^{-1} in IR spectrum. This absorption was not found in **4**. Thus the structure **7** was ruled out in this cyclization.

Experimental

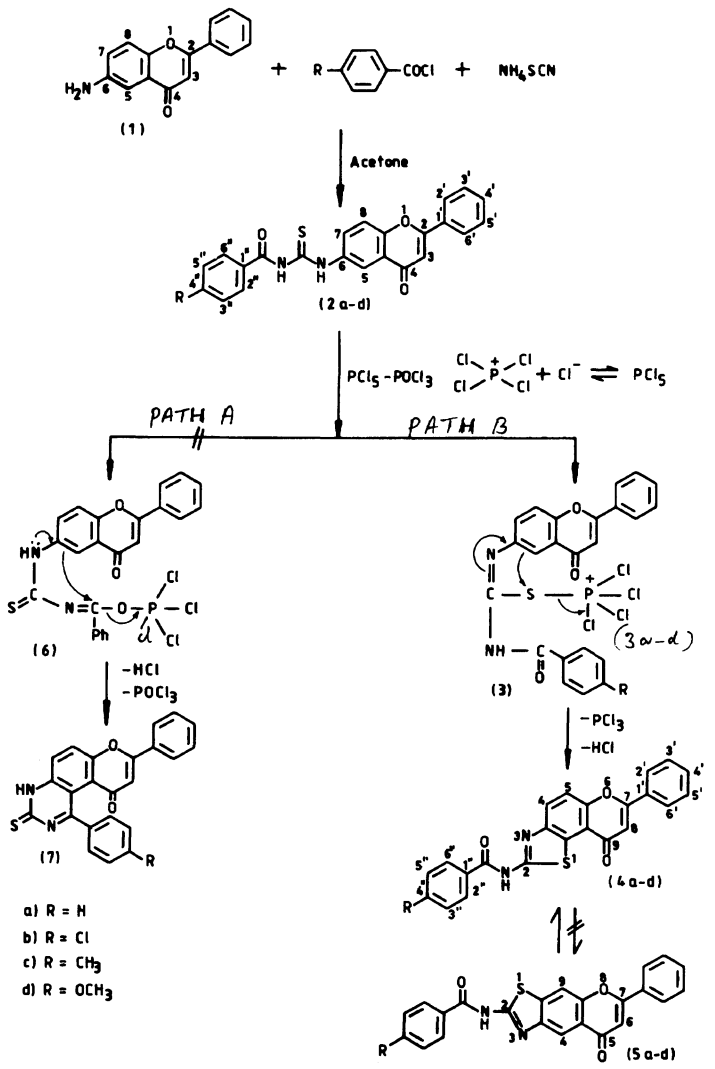
All melting points reported are uncorrected. IR spectra were recorded on a Perkin–Elmer infrared 337 spectrometer. ^1H NMR spectra run on a varian A-60 D (80 MHz) instrument in $CDCl_3$ and CF_3COOD (chemical shifts in δ ppm). The mass spectra were recorded on a UG-Micro mass 7070 H instrument.

General Procedure for Preparation of *N*-Benzoyl-*N'*-(2-phenyl-4-oxo-4*H*-[1]benzopyran-6-yl)thioureas (2a—d). To a solution of ammonium thiocyanate (0.76 g, 0.01 mol) in acetone (20 ml), aroyl chloride (1.40 g, 0.01 mol) was added dropwise with shaking. After heating the mixture on a steam bath for 0.5 h, a solution of 6-aminoflavone (**1**, 2.37 g, 0.01 mol) in acetone (20 ml) was added and refluxed for 2 h. The solvent was distilled off under reduced pressure, the residue treated with water and the solid that separated was filtered, recrystalization from benzene gave colorless crystals **2**. The overall yields are 65—70%.

General Procedure for Preparation of *N*-(9-Oxo-7-phenyl-9*H*-pyrano[2,3-*g*]benzothiazol-2-yl)benzamides (4a—d). To *N*-benzoyl-*N'*-(2-phenyl-4-oxo-4*H*-[1]benzopyran-6-yl)thiourea(**2a**, 1.34 g, 0.003 mol), Phosphoryl chloride (12 ml), and phosphorus pentachloride (0.69 g, 0.003 mol) were added in that order. The mixture was refluxed for 2 h, $POCl_3$ was distilled off under reduced pres-

Table 1. Characterization of *N*-(9-Oxo-7-phenyl-9*H*-pyrano[2,3-*g*]benzothiazol-2-yl)benzamides (**4a**—**d**)

Compound	Mp °C	Molecular formula	Elemental analysis Found(F):Calcd(C) C	H	N	IR(KBr)	^{1}H NMR (CF_3COOD) δ/ppm	MS (m/z) M^+
4a	220 Decomp	$C_{23}H_{14}N_2O_3S$	F: 69.33	3.54	7.05	3250—3000 (br, NH)	7.38 (1H, s, C_8–H)	398
			C: 69.34	3.51	7.03	1620 (benzopyrone carbonyl)	8.02 (1H, d, J=9.5 Hz, C_4–H)	
							8.38 (1H, d, J=9.5 Hz, C_5–H)	
						1668 (amide carbonyl)	7.98 (4H, m, C_2', 6′ & C_2'', C_6''–H)	
							7.50 (6H, m, C_3', 4′, 5′ & C_3'', 4″, 5″–H	
4b	240	$C_{23}H_{13}N_2O_3SCl$	F: 63.86	3.01	6.50	3000—3100 (br, NH)	7.37 (1H, s, C_8–H)	432
			C: 63.88	3.00	6.48	1620 (Benzopyrone carbonyl)	8.01 (5H, m, C_2', 6′ & C_2'', 6″ & C_4–H)	
							8.40 (1H, d, J=9.0 Hz, C_5–H)	
						1665 (amide carbonyl)	7.59 (5H, m, C_3', 4′, 5′& C_3'', 5″–H)	
4c	266	$C_{24}H_{16}N_2O_3S$	F: 69.92	3.90	6.81	3250—3100 (br, NH)	7.24 (1H, s, C_8–H)	412
			C: 69.90	3.88	6.70	1630 (Benzopyrone carbonyl)	8.00 (5H, m, C_2', 6′ & C_2'', 6″ & C_4–H)	
							8.40 (1H, d, J=10 Hz, C_5–H)	
						1667 (amide carbonyl)	7.62 (3H, m, C_3', 4′, 5′–H)	
							7.43 (2H, d, J=8.5 Hz, C_3'', 5″–H)	
							2.52 (3H, s, $-CH_3$)	
4d	232	$C_{24}H_{16}N_2O_4S$	F: 66.30	3.87	6.77	3150—3250 (br, NH)	7.30 (1H, s, C_8–H)	416
			C: 66.34	3.84	6.73	1636 (Benzopyrone carbonyl)	8.03 (5H, m, C_2', 6′ & C_2'', 6″ & C_4–H)	
							8.35 (1H, d, J=9.0 Hz, C_5–H)	
						1665 (amide carbonyl)	7.59 (5H, m C_3', 4′, 5′ & C_3'', 5″–H)	
							3.82 (3H, s, $-OCH_3$)	



Scheme 1.

sure and the residure was poured into crushed ice (100 g). The solid that separated was filtered, on chromatographic purification (silica gel, ACME, 200 mesh) by elution with benzene–ethyl acetate (7 : 3, 300 ml) afforded **4**. The overall yields are 65—70%.

References

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