

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

Mantripragada Narayana RAO, Thota SAMBAIAH, Gazula Levi David KRUPADANAM, and
Gotety SRIMANNARAYANA*

Department of Chemistry, Osmania University, Hyderabad-500007, India

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Synopsis. 6-Aminoflavone¹⁾ (**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 PCl₅ in POCl₃ 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 chemotherapeutic 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-Aminoflavone¹⁾ (**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 C₂₃H₁₆N₂O₃S. 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 (CDCl₃) δ=6.80 (1H, s, C₃-H), 8.38 (1H, d, *J*=1.95 Hz, C₅-H), 7.22 (1H, m, C₇-H), 7.36 (1H, m, C₈-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 PCl₅ in POCl₃ 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 C₂₃H₁₄N₂O₃S (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 (CF₃COOD) revealed AB doublets at δ=8.02 (C₄-H, *J*=9.5 Hz) and 8.38 (C₅-H, *J*=9.5 Hz) which indicated the fusion is angular (**4a—d**). The C₈-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 PCl₅ in POCl₃ 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 C₆ 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 took 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

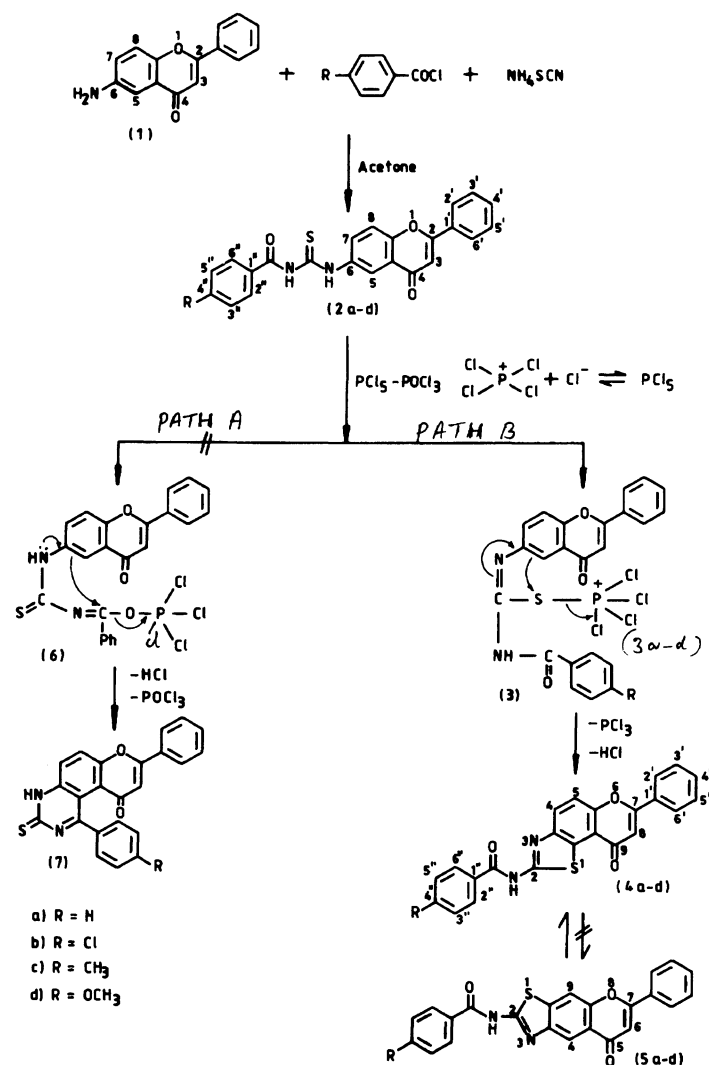
All melting points reported are uncorrected. IR spectra were recorded on a Perkin-Elmer infrared 337 spectrometer. ¹H NMR spectra run on a varian A-60 D (80 MHz) instrument in CDCl₃ and CF₃COOD (chemical shifts in δ ppm). The mass spectra were recorded on a UG-Micro mass 7070 H instrument.

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, recrystallization 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, POCl₃ 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)			IR(KBr)	¹ H NMR (CF ₃ COOD) δ/ppm	MS (<i>m/z</i>) M ⁺
			C	H	N			
4a	220 Decomp	C ₂₃ H ₁₄ N ₂ O ₃ S	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, <i>J</i> =9.5 Hz, C ₄ —H) 8.38 (1H, d, <i>J</i> =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 ₂ O ₃ SCl	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, <i>J</i> =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 ₂ O ₃ S	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, <i>J</i> =10 Hz, C ₅ —H)	
						1667 (amide carbonyl)	7.62 (3H, m, C ₃ ['] , 4 ['] , 5 ['] —H) 7.43 (2H, d, <i>J</i> =8.5 Hz, C ₃ ^{''} , 5 ^{''} —H) 2.52 (3H, s, —CH ₃)	
4d	232	C ₂₄ H ₁₆ N ₂ O ₄ S	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, <i>J</i> =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 residue 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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