

Synthesis of some new 4-Heteroaryl substituted 3-cyano coumarins starting from 3-formylchromones

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Abstract

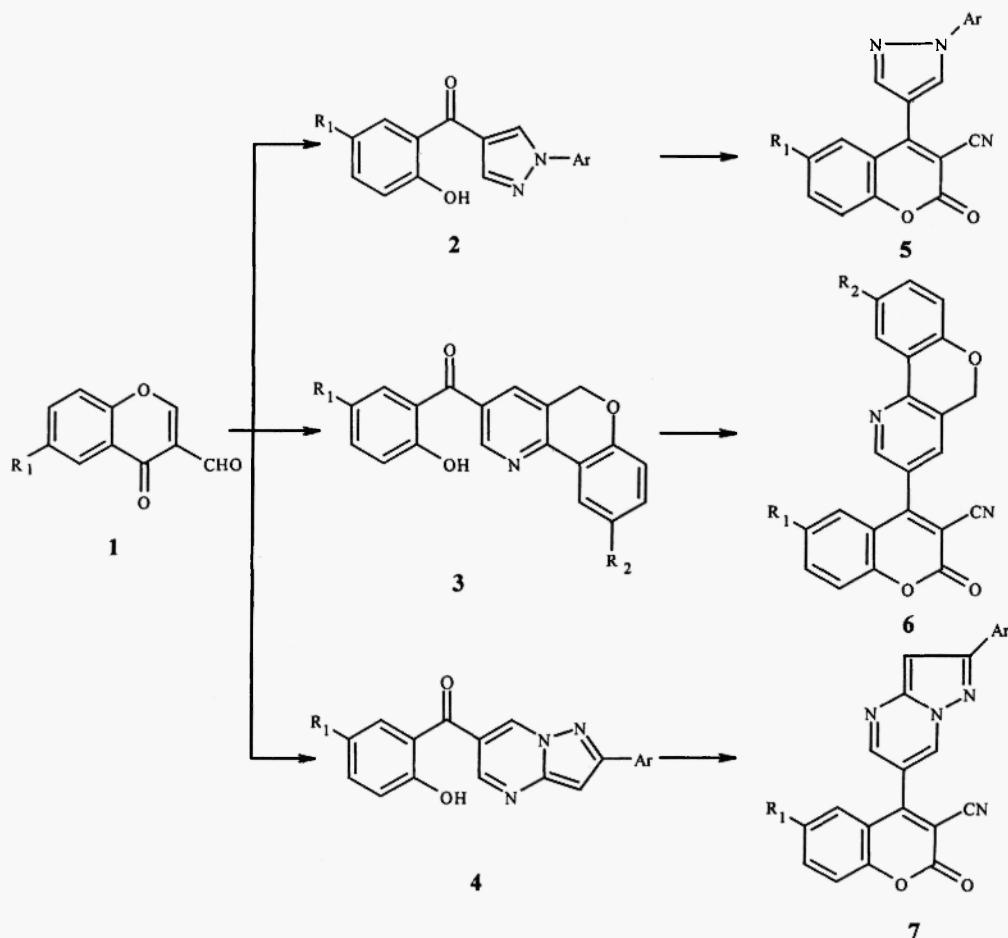
A series of new 4-pyrazolyl/benzopyrano[4,3-*b*]pyridinyl/pyrazolo[1,5-*a*]pyrimidinyl-3-cyanocoumarins (**5**, **6** & **7**) have been synthesized starting from 3-formylchromones (**1**).

Introduction

Coumarins, continue to be compounds of considerable interest because of their application as medicinal agents¹. Coumarins are widely distributed in nature and exhibit various biological activities². Among synthetic coumarins, those with a substituent at position 3 occupy special place because of their pharmacological activities such as anthelmintic, hypnotic, insecticidal and anticoagulant properties³⁻⁵. Furthermore, heterocycles like pyrazoles⁶, benzopyranopyridines⁷ and pyrazolopyrimidines⁸ form part of many therapeutic agents. 3-Formylchromones are versatile intermediates and can be readily converted into 2'-hydroxyheteroarylketones⁹. Earlier publication from these laboratories described the synthesis of 3-heterosubstituted-1,2-benzisoxazoles. In continuation of our interest on the synthetic utility of 3-formylchromones¹¹, we herein report the synthesis of some new 3-cyanocoumarins with a heteroaryl substituent at position 4.

Results and Discussion

The required starting materials, 4-(2'-hydroxybenzoyl)pyrazoles (**2**) and 3-(2'-hydroxybenzoyl)-5*H*[1]-benzopyrano[4,3-*b*]pyridines (**3**) were readily obtained from 3-formylchromones (**1**) as reported earlier¹⁰. 6-(2'-hydroxybenzoyl)pyrazolo[1,5-*a*]pyrimidines (**4**) were obtained by reaction of **1** with 3-aryl-5-amino-1*H*-pyrazoles in refluxing ethanol according to the method described by Quiroga et.al¹². The hydroxyketones **2**, **3** & **4** were condensed with ethyl cyanoacetate in refluxing methanol in presence of catalytic amount of sodium methoxide (Scheme 1). All the products **5**, **6** and **7** were characterized by IR and ¹H NMR spectra. Thus the products **5**, **6** and **7** exhibited characteristic absorption around 2220 - 2230 cm⁻¹ for nitrile group and around 1720 - 1730 cm⁻¹ for coumarin carbonyl group respectively. ¹H NMR spectra of **5**, **6** & **7** exhibited characteristic signals for the respective heterocycles apart from other aromatic protons. For example, ¹H NMR spectrum of compound **5a** exhibited two multiplets at δ 7.5(5H, ArH), 7.8(4H, ArH) and two singlets at δ 8.1 and 8.5 ppm for pyrazole protons.



SCHEME 1

The structures of products have been characterized by analytical data supported by Mass spectra of representative compounds (Table 1).

Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra recorded in KBr pellets. ^1H NMR spectra on a Varian 200MHz instrument with TMS as internal standard. Chemical shifts are expressed in δ ppm and Mass spectra on a Hewlett Packard Mass spectrometer operating at 70ev.

General procedure for the preparation of 4

A mixture of 6-fluoro-3-formylchromone (**1**, $\text{R}_1 = \text{F}$, 0.05 mol) and 3-phenyl-5-aminopyrazole (0.05 mol) in absolute ethanol (50 ml) was stirred at reflux for 1 hr. The precipitated product was filtered, washed with ethanol and recrystallized from ethanol to give pure **4** as yellow crystalline solids.

6-(5-Fluoro-2-hydroxybenzoyl)-2-phenylpyrazolo[1,5-a]pyrimidine 4a (R₁=F, R₂=H)

This was prepared in 85% yield according to the general procedure described above. m.p: 234°C, IR (KBr): 1700 cm⁻¹ (C=O) m.s (70ev) m/z (%): 333 (M⁺, 78%), 195(100%), 139(20%), 77(26%), ¹H NMR (200 MZ, DMSO-d₆): δ 10.4(bs, 1H), 9.1(s, 1H), 8.78(s, 1H), 7.98(d, 2H), 7.0-7.5(m, 7H). Anal calcd for C₁₉H₁₂FN₃O₂, C, 68.46; H, 3.60; N, 12.61%. found: C, 68.23; H, 3.81; N, 12.76%.

General procedure for the preparation of 4-substituted 3-cyanocoumarins: (5,6 & 7)

A mixture of 2'-Hydroxy ketone (5 or 6 or 7, 0.1 ml), ethylcyanoacetate (0.15 mol) and sodium methoxide (0.015 mol) in methanol (100 ml) was refluxed for 2 hrs. The reaction mixture was cooled, filtered, washed with methanol and recrystallized from methanol to give pure 5, 6 & 7 as yellow crystalline solid.

4-(1-Phenylpyrazol-4-yl)-3-cyanocoumarins 5a:

2'-Hydroxyketone(2, R₁ = H) was converted into 5a according to the general procedure described above to give 5a as yellow crystalline solid 56%. M.p: 201°C; ms (70ev) m/z (%): 313(M⁺, 100%). ¹H NMR (CDCl₃, 200 MZ): δ 7.4-7.6(m, 5H, ArH), 7.7-7.9(m, 4H, ArH), 8.15(s, 1H, H_{pyr}), 8.8(s, 1H, H_{pyr}) Found: C, 72.67; H, 3.83; N, 13.26 C₁₉H₁₁N₃O₂ requires C, 72.84; H, 3.51; N, 13.41.

Table 1: Physical data of cyanocoumarins 5, 6 & 7

Compound	R ₁	R ₂	Ar	Yield %	m.p°C	Mol. Formula
5a	H	-	C ₆ H ₅	56	201	C ₁₉ H ₁₁ N ₃ O ₂
5b	CH ₃	-	C ₆ H ₅	62	239	C ₂₀ H ₁₃ N ₃ O ₂
5c	F	-	C ₆ H ₅	67	199	C ₁₉ H ₁₀ FN ₃ O ₂
5d	Br	-	C ₆ H ₅	64	287	C ₁₉ H ₁₀ BrN ₃ O ₂
6a	H	H	-	53	235	C ₂₂ H ₁₂ N ₂ O ₃
6b	CH ₃	F	-	57	259	C ₂₃ H ₁₃ FN ₂ O ₃
6c	Cl	H	-	59	268	C ₂₂ H ₁₁ ClN ₂ O ₃
6d	Br	H	-	61	263	C ₂₂ H ₁₁ BrN ₂ O ₃
7a	F	-	C ₆ H ₅	72	>300	C ₂₂ H ₁₁ FN ₄ O ₂
7b	F	-	4-CH ₃ C ₆ H ₄	65	>300	C ₂₂ H ₁₃ FN ₄ O ₂
7c	F	-	4-CH ₃ OC ₆ H ₄	73	>300	C ₂₂ H ₁₃ FN ₄ O ₃
7d	F	-	4-ClC ₆ H ₄	77	>300	C ₂₂ H ₁₀ ClFN ₄ O ₂

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13. ¹H NMR spectral data of representative compounds: **5b** (CDCl₃, 200 MHz): δ 2.4(s, 3H, CH₃), 7.4(m, 5H, ArH), 7.6(m, 3H, ArH), 8.05(s, 1H, H_{pyr}), 8.7(s, 1H, H_{pyr}). **6a** (CDCl₃, 200 MHz): δ 5.4(s, 2H, OCH₂), 7.0-7.6(m, 8H, ArH), 7.8(dd, 1H, H_{pyr}), 8.3(dd, 1H, H_{pyr}). **7b** (DMSO-d₆, 200 MHz): δ 2.4(s, 3H, CH₃), 6.4(s, 1H, H_{pyr}), 7.0(m, 3H, ArH), 7.2(d, 2H, ArH), 7.9(d, 2H, ArH), 8.15(d, 1H, H_{pym}), 8.4(s, 1H, H_{pym}).

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