

Synthesis of Pyrazolo[1,5-a]pyrimido[4,3-d]benzopyrans and 2-Pyrazolo[1,5-a]pyrimidinylphenols from the reaction of 5(3)-amino pyrazoles

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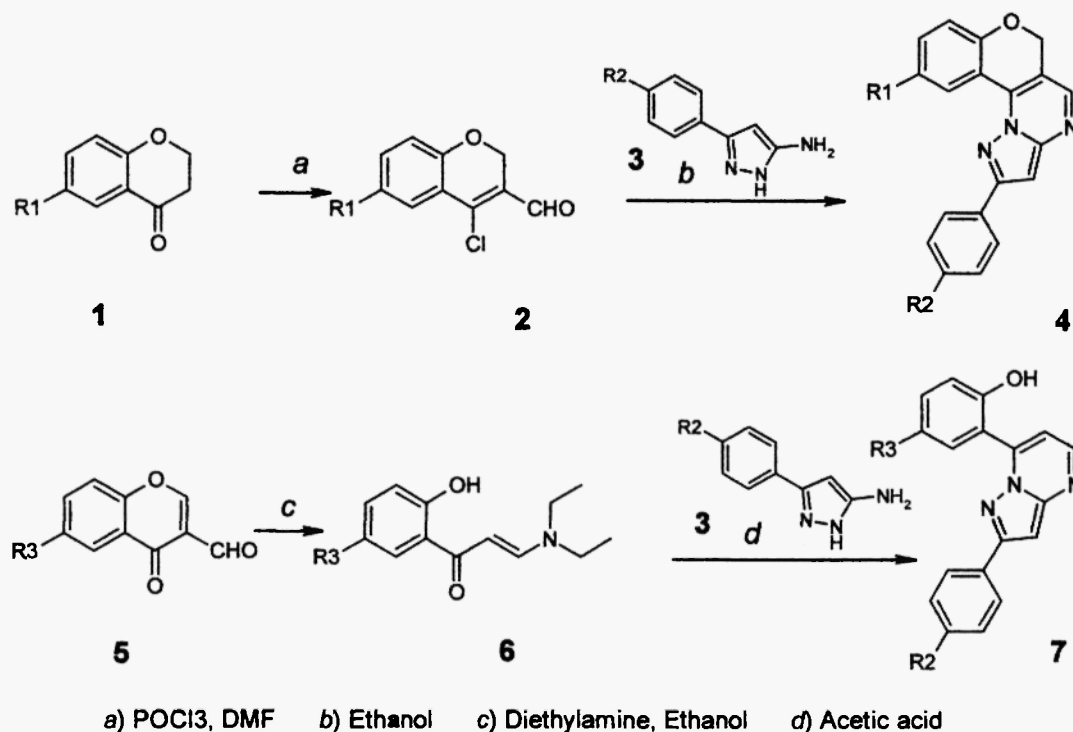
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Abstract

A number of Pyrazolo[1,5-a]pyrimido[4,3-d]benzopyrans(**4a-m**) and 2-(Pyrazolo[1,5-a]pyrimidinyl)phenols (**7a-k**) have been prepared from the reaction of 5(3)-aminopyrazoles **3**.

Introduction

Several benzopyrans and benzopyrans fused with a heterocyclic ring at 3,4 positions such as pyridine, pyrazole and isoxazoles have been reported to possess



SCHEME -1

diverse types of pharmacological properties¹⁻⁴. Recently, synthesis of pyrazolo[1,5-a]pyrimidine derivatives gained considerable interest because of their physiological and biological activities⁵⁻⁸. In view of this, and in continuation of our work on chromone based heterocycles⁹, we report herein the synthesis of some new pyrazolopyrimidobenzopyrans (4) and 2-pyrazolopyrimidinylphenols making use of the bifunctional nucleophilic nature of 5(3)-aminopyrazoles (3) (Scheme -1).

Reaction of benzopyran-4-ones(1) with dimethylformamide and phosphorous oxychloride under Vilsmeier reaction conditions gave 4-chlorobenzopyran-3-carboxaldehydes(2) in very good yields¹⁰. Refluxing 2 with 5-Amino-3-arylpyrazoles (3) in ethanol gave the desired pyrazolopyrimidobenzopyrans 4 in good yields as yellow crystalline solids. The structure of 4 was based on spectral data (IR, NMR and Mass). Thus, the absence of NH₂ and C=O absorption bands in the IR spectra of 4 indicate the condensation of amino group of 5-aminopyrazole with carboxaldehyde group to form the intermediate Schiff's base, which undergoes spontaneous cyclization with 4-chloro group of 2 with pyrazole NH under the reaction conditions to give 4. This is further supported by ¹H-NMR spectra of 4 which showed a singlet around δ 5.0 for -OCH₂ group of benzopyran along with other aromatic pyrazole and pyrimidine protons.

The enaminoketones 6 are an important class of synthons which can be elaborated to a wide variety of heterocycles¹¹. Especially, these are very useful in the synthesis of 2-heterocyclicsubstituted phenols¹², which are otherwise difficult to synthesize by conventional methods. The enaminoketones are readily obtained from substituted 3-formylchromones(5) in a single step by treatment with diethylamine in refluxing ethanol. 6 on reaction with 5-aminopyrazoles (3) in refluxing acetic acid gave the desired 2-pyrazolo[1,5-a]pyrimidinylphenols 7 in moderate yields. ¹H-NMR spectra of 7 exhibited signals for aromatic OH, pyrimidine, pyrazole and other aromatic protons, which were further confirmed by IR and Mass spectra.

Thus the present method offers a convenient one step synthesis of pyrazolopyrimidobenzopyrans(4) and pyrazolo[1,5-a]pyrimidinylphenols(7) from 5(3)-aminopyrazoles(3).

The structures of all the compounds reported in Table 1 were based on their IR, NMR and correct elemental analyses.

Table-1: Physical constants of chemical transformations shown in Scheme -1

Compound	R ₁	R ₂	R ₃	4		7	
				m.p °C	Yield%	m.p °C	Yield %
a	H	H	H	213	60	154	42
b	H	Cl	H	235	62	218	45
c	H	CH ₃	H	224	65	184	51
d	Cl	H	Cl	214	61	174	38
e	Cl	Cl	Cl	209	48	238	52
f	Cl	OCH ₃	Cl	225	62	194	61
g	F	H	NO ₂	224	63	283	80
h	F	Cl	NO ₂	220	58	288	88
i	F	CH ₃	NO ₂	228	52	272	92
j	F	OCH ₃	NO ₂	208	56	278	97
k	CH ₃	OCH ₃	CH ₃	198	57	217	55
l	CH ₃	H	-	198	50	-	-
m	CH ₃	Cl	-	202	80	-	-

Experimental Section

Melting points were determined in open capillaries and are uncorrected. The purity of all the compounds was routinely checked by TLC on silica gel coated plates. IR spectra was recorded in KBr pellets, ¹H-NMR spectra on a varian 200 MHz instrument with TMS as internal standard and chemical shifts expressed in δ ppm and Mass spectra on a Hewlett packard Mass spectrometer operating at 70ev.

General procedure for the preparation of 4-chloro-3-benzopyran-3-carboxaldehydes(2).

To a mixture benzopyran-4-one (1, 0.01 mole) and dimethylformamide (0.04 mole) was added phosphorous oxychloride (0.02 mole) drop wise maintaining the temperature at 5°C. It was maintained for 1 hr at 5°C and 1 hr at 60°C and it was cooled, poured onto crushed ice, the separated solid was filtered, washed with water and dried. The compounds are sufficiently pure on TLC and were used without further purification.

2-(4Methylphenyl)-pyrazolo[1,5-a]pyrimido[4,3-d]benzopyran(4c).

A mixture of 4-chloro-benzopyran 3-carboxaldehyde (2a, R₁=H, 1.94 gm, 0.01 mole) and 3-(4-methylphenyl)5-aminopyrazole (3, R₂=CH₃, 1.73gm, 0.01 mole) in ethanol (10 ml) was refluxed for 4 hr. The reaction was monitored by TLC. It was cooled, and the separated solid was filtered, washed with ethanol and recrystallized from ethanol to give pure 4c. Yield. 2.02 gm (65 %). m.p. 224°C. ms(70ev) m/z(%) 312(14, M⁺). ¹H-NMR (CDCl₃ + DMSO-d₆) : δ 2.4(s, 3H, ArCH₃); 5.20(s, 2H, -OCH₂); 6.8(s, 1H, Hpyr); 6.9(d, 1H, ArH); 7.1-7.2(m, 4H, ArH), 7.8(d, 2H, ArH); 8.35(d, 1H,

ArH); 8.45(s, 1H, H pym) (found: C, 76.71; H, 4.82; N, 13.42 C₂₀H₁₅N₃O requires C, 76.67; H, 4.79; N, 13.41%).

2'-[(4-Methoxyphenyl)pyrazolo[1,5-a]pyrimidin-7-yl]-4'-chlorophenol (7c).

A mixture of enaminoketone (6, R₁=Cl, 2.25g, 0.01 mole), 3-(4-methoxyphenyl)-5-aminopyrazole (3, R₂=OCH₃, 1.89 gm, 0.01 mole) in glacial acetic acid (10 ml) was refluxed for 4 hrs. The reaction was monitored by TLC. It was cooled and poured onto crushed ice. The separated solid was filtered and washed with water. It was purified by column chromatography with ethylacetate-hexane(1:4) as eluent to give pure 7c as crystalline solid. Yield: 2.14 gm (61%) ms(70ev) m/z(%) 351(100%) 307(20%) 289(20%) 154(80%) 136(50%) m.p.194°C, ¹H-NMR (CDCl₃): δ 3.8 (s, 3H, OCH₃); 6.8-7.1 (m, 5H, ArH); 7.4(dd, 1H, ArH); 7.6(s, 1H, H pym); 7.9(d, 2H, ArH); 8.5(s, 1H, H pym) 10.0(s, 1H, -OH) (found: C, 64.84, H, 4.01, N, 11.98 C₁₉H₁₄ClN₃O₂ requires C, 64.86, H, 3.98; N, 11.94%)

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13. Representative ¹H-NMR spectra: **4a** (CDCl₃ + DMSO-d₆): δ 5.2(s, 2H, OCH₂); 6.85(s, 1H, Hpyr); 7.0(m, 2H, ArH); 7.4(m, 4H, ArH); 7.95(d, 2H, ArH); 8.22(d, 1H, ArH); 8.7(s, 1H, CH=N). **4f** (DMSO-d₆): δ 3.9(s, 3H, OCH₃); 5.35(s, 2H, OCH₂); 7.0(m, 4H, ArH); 7.41(m, 1H, ArH); 7.9-8.2(m, 3H, ArH); 8.8(s, 1H, CH=N). **4i** (CDCl₃+DMSO-d₆): δ 2.4(s, 3H, ArCl₃); 5.23(s, 2H, OCH₂); 6.87(s, 1H, Hpyr); 7.0(m, 4H, ArH); 7.9(m, 3H, ArH); 8.8(s, 1H, CH=N).

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