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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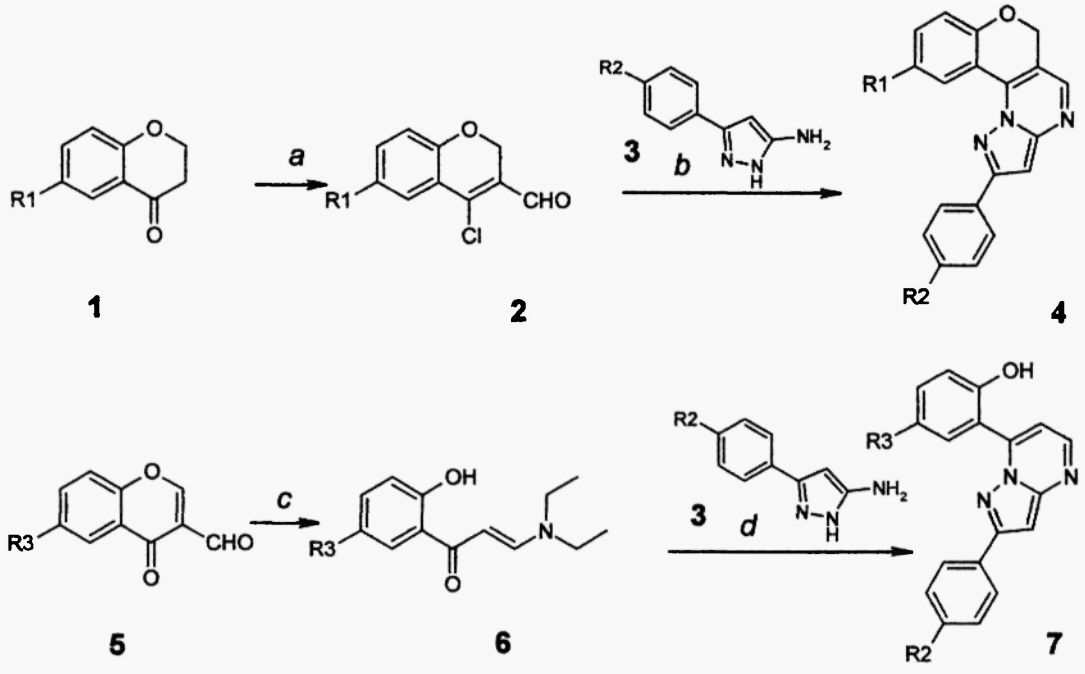
Abstract

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



a) POCl3, DMF *b*) Ethanol *c*) Diethylamine, Ethanol *d*) Acetic acid

SCHEME -1

diverse types of pharmacological properties[1-4]. Recently, synthesis of pyrazolo[1,5-a]pyrimidine derivatives gained considerable interest because of their physiological and biological activities[5-8]. In view of this, and in continuation of our work on chromone based heterocycles[9], 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 Vilsmeyer reaction conditions gave 4-chlorobenzopyran-3-carboxaldehydes(**2**) in very good yields[10]. 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 NH_2 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 Schiffs'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 ^{1}H-NMR spectra of **4** which showed a singlet around δ 5.0 for $-OCH_2$ 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 heterocycles[11]. Especially, these are very useful in the synthesis of 2-heterocyclicsubstituted phenols[12], 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. ^{1}H-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 elemented analyses.

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

				4		7	
Compound	R_1	R_2	R_3	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	OCH3	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, ^{1}H-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 Hewelett packard Mass spectrometer opreating 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**, R_1=H, 1.94 gm, 0.01 mole) and 3-(4-methylphenyl)5-aminopyrazole (**3**, R_2=CH_3, 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^+). ^{1}H-NMR ($CDCl_3$ + DMSO-d_6) : δ 2.4(s, 3H, $ArCH_3$); 5.20(s, 2H, -OCH_2); 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, 482; N, 13.42 $C_{20}H_{15}N_3O$ 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**, R_1=Cl, 2.25g, 0.01 mole), 3-(4-methoxyphenyl)-5-aminopyrazole (**3**, R_2=OCH_3, 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, ^{1}H-NMR ($CDCl_3$): δ 3.8 (s, 3H, OCH_3); 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 $C_{19}H_{14}ClN_3O_2$ requires C, 64.86. H, 3.98; N, 11.94%)

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13. Representative ^{1}H-NMR spectra: **4a** ($CDCl_3$ + DMSO-d_6): δ 5.2(s, 2H, OCH_2); 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-d_6): δ 3.9(s, 3H, OCH_3); 5.35(s, 2H, OCH_2); 7.0(m, 4H, ArH); 7.41(m,1H, ArH); 7.9-8.2(m, 3H, ArH); 8.8(s, 1H, CH=N). **4i** ($CDCl_3$+DMSO-d_6): δ 2.4(s, 3H, $ArCl_3$); 5.23(s, 2H, OCH_2); 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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