Synthesis of 7-Aryl / chromonyl substituted benzopyrano[4,3-d]pyrazolo[1,5-a]pyrimidines by reaction of 5(3)-Aminopyrazoles

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Abstract

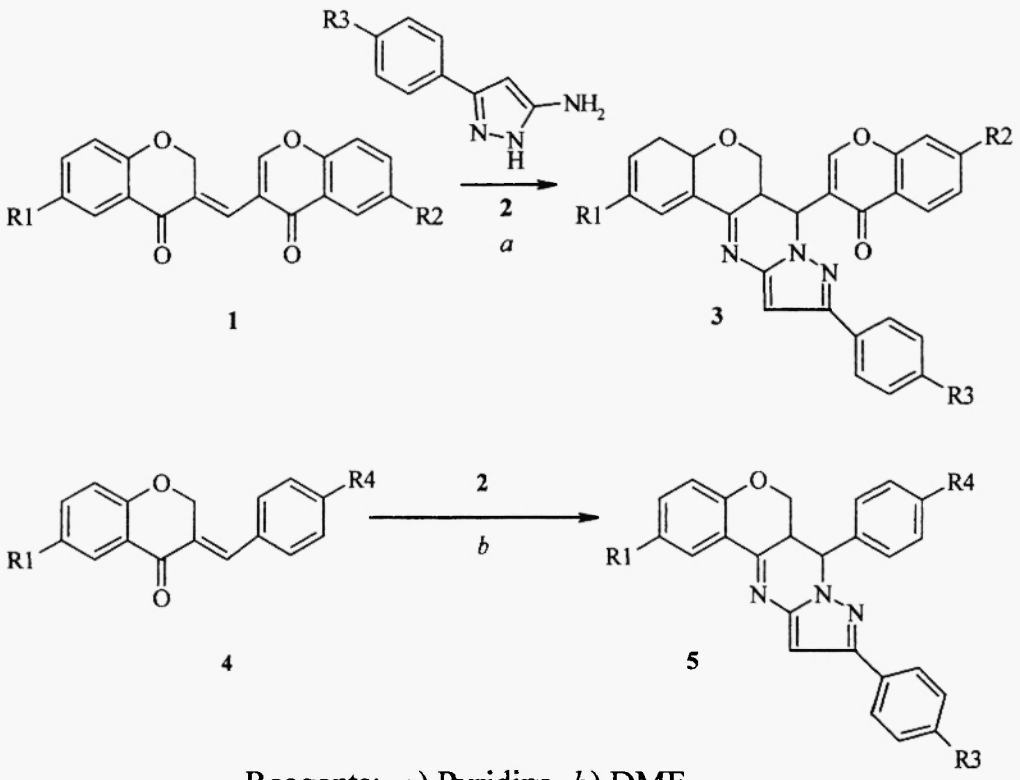
A series of 7-Aryl/chromonyl substituted benzopyrano[4,3-d]pyrazolo[1,5-a]pyrimidines (**3a-g** and **5a-c**) have been prepared by reaction of 5(3)-Aminopyrazoles(**2**).

Introduction

The Synthesis of pyrazolo[1,5-a]pyrimidines gained considerable importance over the last one decade because of the diverse types of biological activities exhibited by the system[1-3]. Also, several benzopyran derivatives have been reported as potential pharmaceutical agents[4-5]. It is known that heterocyclic amines such as aminopyrazoles react with α, β unsaturated carbonyl compounds to give fused heterocyclic ring system[6-8]. Especially, 5(3)-aminopyrazoles with an exocyclic amino group and a highly reactive nucleophilic ring nitrogen are very important intermediates and have been extensively used in the synthesis of pyrazolo[1,5-a]pyrimidines[9]. Earlier communication from these laboratories described the synthesis of new chromone substituted benzopyranopyridines making use of the α, β unsaturated ketone system present in the 3-(4-oxo-4H-benzopyrano-3-methynyl)-2,3-dihydro-4H-benzopyran-4-one frame work[10]. In continuation of this work and in view of the biological activity exhibited by pyrazolo[1,5-a]pyrimidines and benzopyrans, we now report the synthesis of pyrazolo[1,5-a] pyrimidines additionally fused with a benzopyran ring with a chromone substitution, making use of the reaction of 5(3)-aminopyrazoles.

Results and Discussion

The starting materials **1** & **4** required in the present work were prepared according to the reported methods[11]. Thus reaction of 2,3-dihydrobenzopyranone with 3-formylchromone in refluxing ethanol in presence of triethylamine gave benzopyranomethynyl benzopyranones(**1**). 3-Arylidenebenzopyranones(**4**) were prepared by reaction of 2,3-dihydrobenzopyranone with Araldehydes in methanolic hydrochloric acid. 3-Aryl-5-aminopyrazoles(**2**) required in the present work were prepared by reaction of benzoylacetonitrile with hydrazine hydrate according to known method[12].



Reagents: *a*) Pyridine *b*) DMF

SCHEME-1

The synthesis of title compounds **3** & **5** was achieved by reacting **1** which is having a α, β unsaturated carbonyl system with carbonyl group forming part of the benzopyran ring and α, β-unsaturated system exocyclic to carbonyl group, with 3-Aryl5-aminopyrazoles (**2**) in pyridine at 100° to give 7-chromon-3-ylbenzopyrano[4,3-d]pyrazolo[1,5-a]pyrimidine (**3**) in moderate yields. Similarly reaction of **4** with **2** in dimethylformamide gave 7-aryl-benzopyrano[4,3-d]pyrazolo[1,5-a]pyrimidine (**5**). Compounds **3** & **5** were purified by column chromatography and were characterized by IR, ^{1}H-NMR and Mass spectra. The basic support for the structures of **3** & **5** was provided by ^{1}H-NMR spectra which prove the presence of building block -OCH_2(C-6)-CH(C-6a)-CH(C-7)N. Thus the –OCH_2 proton of benzopyran ring which appeared as a singlet at δ 5.1 in the starting material changed to a multiplet at δ 4.6. The C-7 proton appeared as a doublet at 5.86 and C-6a proton as a multiplet at δ 3.72. This was further supported by IR (1680 cm^{-1}, C=O of chromone) and mass spectra. Thus the compounds **3** & **5** result from condensation between amino group of 5-aminopyrazole with carbonyl group of **1** followed by Michael addition on the double bond by the pyrazole ring nitrogen.

The structures of all the compounds reported in Table -1 were established, based on their IR, ^{1}H-NMR and correct elemental analyses. Thus the present work offers a new

reaction of 5-aminopyrazoles with α, β-unsaturated ketone system which form part of the ring leading to the formation of fused pyrazolo[1,5-a]pyrimidines.

Experimental

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 Hewlett Packard Mass spectrometer operating at 70ev.

General procedure for the preparation of 3

A mixture of **1** (0.01 mole) and **2** (0.01 mole) in pyridine (10 ml) was heated to 100° for 4 hrs. The progress of the reaction was monitored by TLC. It was poured onto cold water (100 ml), the separated solid was filtered, washed with water, dried and purified by column chromatography to give **3**.

General procedure for the preparation of 5

A mixture of **4** (0.01 mole) and **2** (0.01 mole) in Dimethylformamide (10 ml) was heated to 100° for 4 hrs. The progress of the reaction was monitored by TLC. It was poured onto cold water (100 ml), the separated solid was filtered, washed with water, dried and purified by column chromatography to give **5**.

7-(6-Methyl-4-oxo-chromon-3-yl)-10-(4'-chlorophenyl)-6a,7-dihydro-6H-benzo-pyrano[4,3-d]pyrazolo[1,5-a]pyrimidine (3a)

A mixture of 3-(6'-methyl-4-oxo-4H-benzopyranomethynyl)-2,3-dihydro-4H-benzopyran-4-one (**1a**, R_1=H, R_2=CH_3, 3.18 g, 0.01 mole) and 3-(4'-chlorophenyl)-5-aminopyrazole (**2**, R_3=Cl, 1.935 gm, 0.01 mole) in pyridine (10 ml) was heated to 100° for 4 hrs. The progress of the reaction was monitored by TLC. It was poured onto cold water (100 ml), the separated solid was filtered and washed with water (2 x 50 ml). The product was purified by column chromatography on silica gel (Hexane: ethylacetate, 4:1) to give pure **3a** as yellow crystalline solid. Yield: 2.61gm (53%); m.p. 246°; IR: 1680 cm^{-1} (C=O, chromone) ms (70ev) m/z (%); 494(M^+, 29%), 346(32%), 307(36%), 207(20%), 154(100%), 137(66%). ^{1}H-NMR($CDCl_3$): δ 2.5 (s, 3H, CH_3); 3.25(m, 1H, C_{6a}-H); 4.7(m, 2H, -OCH_2); 5.9(d, 1H, C_7-H); 7.0(m, 3H, ArH); 7.3(m, 2H, ArH); 7.5(m, 3H, ArH); 7.9(m, 3H, ArH); 8.1(s, 1H, Hpyr), 9.4(s, 1H, chromone H). (Found: C, 70.49; H, 4.02; N, 8.53 $C_{29}H_{20}ClN_3O_3$ requires C, 70-51; H, 4.05; N, 8.51%).

Compounds **3b-g** reported in Table -1 were similarly prepared.

TABLE -1: PHYSICAL CONSTANT OF CHEMICAL TRANSFORMATIONS SHOWN IN SCHEME -1

Compound	R_1	R_2	R_3	R_4	Yield %	m.p °C
3a	H	CH_3	Cl	-	53	246°
3b	F	Br	OCH_3	-	51	175°
3c	Br	F	OCH_3	-	54	201°
3d	CH_3	CH_3	Cl	-	53	211°
3e	CH_3	F	CH_3	-	57	205°
3f	CH_3	Br	OCH_3	-	55	207°
3g	CH_3	Cl	Cl	-	54	206°
5a	CH_3	-	OCH_3	Cl	49	249°
5b	F	-	OCH_3	CH_3	51	235°
5c	H	-	OCH_3	Cl	48	237°

2-Fluoro-7-(4'-methylphenyl)-10-(4'-methoxyphenyl)-6a,7-dihydro-6H-benzopyrano [4,3 -d]pyrazolo[1,5]pyrimidine (5b, R_1=F, R_3=OCH_3, R_4=CH_3)

A mixture of 6-fluoro-3-(4'-methylbenzylidene)-4H-2,3-dihydrobenzopyran-4-one(**4**, R_1=F, R_4=CH_3, 2.68gm, 0.01 mole) and 3-(4'-methoxyphenyl)-5-aminopyrazole(**2**, R_3=OCH_3, 1.89gm, 0.01 mole) in dimethylformamide (10 ml) was heated to 100° for 4 hrs. The progress of the reaction was monitored by TLC. It was poured onto cold water (100 ml), the separated solid was filtered and washed with water (2 x 50 ml). It was purified by column chromatography (Hexane: ethylacetate, 4:1) to give pure **5b** as yellow crystalline solid. Yield: 2.24gm (51%); m.p: 235°; ms (70ev) m/z (%): 439(M^+, 12%). ^{1}H-NMR($CDCl_3$): δ 2.4 (s, 3H, CH_3); 3.41(m, 1H, C_{6a}-H); 3.8(s, 3H, OCH_3); 4.15(m, 2H, -OCH_2); 4.8(dd, 1H, C_7-H); 6.6(s, 1H, Hpyr); 6.8(m, 3H, ArH); 7.1(m, 1H, ArH); 7.22(m, 4H, ArH); 7.6(m, 2H, ArH); 7.9(m, 1H, ArH). (Found: C, 73.81; H, 4.98; N, 9.54 $C_{27}H_{22}FN_3O_2$ requires C, 73.82; H, 5.01, N, 9.56%)

Compounds **5a** & **5c** reported in Table –1 were similarly prepared.

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13. Representative ^{1}H-NMR Spectra: **3c** ($CDCl_3$): δ 3.2(m, 1H, C_{6a}-H); 3.8(s, 3H, CH_3); 4.65(m, 2H, C_6-H); 5.85(d, 1H, C_7-H); 7.0-8.0(m, 11H, aromatic and pyrazole) 9.8(s, 1H, chromone). **3g** ($CDCl_3$): δ 2.4(s, 3H, CH_3); 3.25(m, 1H, C_{6a}-H); 4.7(m, 2H, C_6-H); 5.85(d, 1H, C_7-H); 7.0-8.0(m, 11H, aromatic and pyrazole); 9.5(s, 1H, chromone H). **5a** ($CDCl_3$): δ 2.4(s, 3H, CH_3); 3.4(m, 1H, C_{6a}-H); 3.8(s, 3H, OCH_3); 4.17(m, 2H, C_6-H); 4.8(d, 1H, C_7-H); 6.6(s, 1H, Hpyr); 6.8-7.9(m, 11H, aromatic).

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