

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

G. Jagath Reddy *, D. Latha, S. Sailaja and K. Srinivasa Rao

R & D Laboratories, Dr. Jagath Reddy's Heterocyclics, 81, S.V.Co-op Industrial Estate, Balanagar, Hyderabad – 500 037, India. E-mail: jagathreddy@usa.net; Fax # 91-40-23773487.

and

Md. Khalilullah

Department of Chemistry, Jawaharlal Nehru Technological University, Hyderabad-500072, India.

Abstract

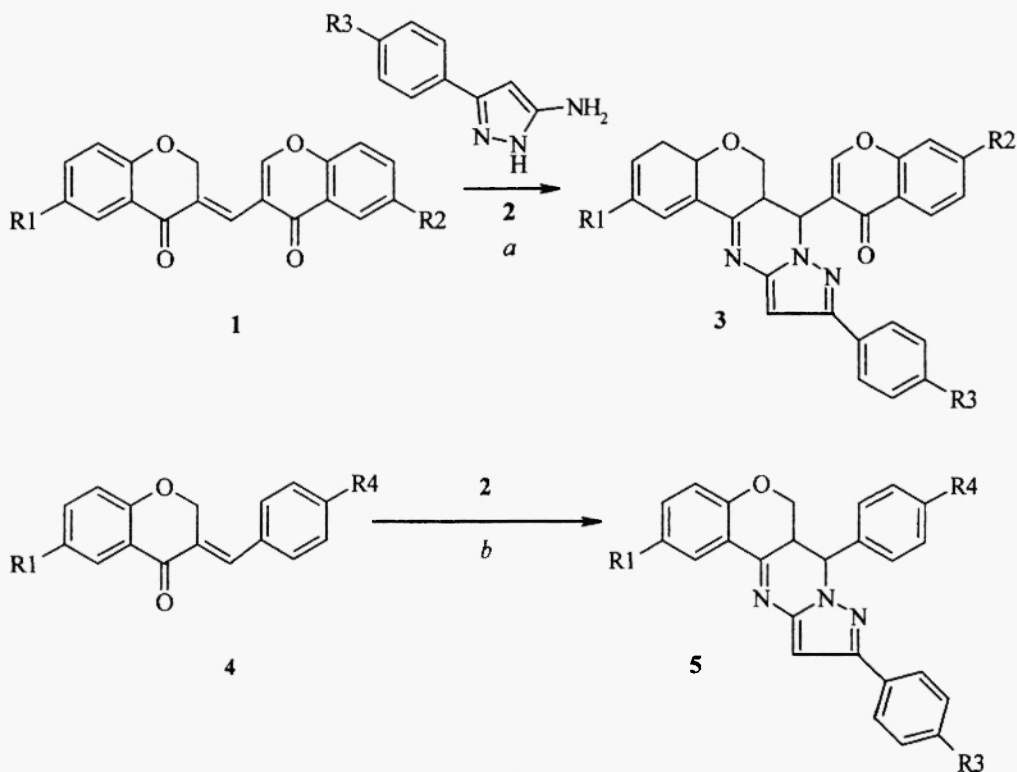
A series of 7-Aryl/chromonyl substituted benzopyrano[4,3-d]pyrazolo[1,5-a]pyrimidines (**3a-g** and **5a-c**) have been prepared by reaction of 5(3)-Aminopyrazoles(**2**).

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 system¹⁻³. Also, several benzopyran derivatives have been reported as potential pharmaceutical agents⁴⁻⁵. It is known that heterocyclic amines such as aminopyrazoles react with α , β unsaturated carbonyl compounds to give fused heterocyclic ring system⁶⁻⁸. 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]pyrimidines⁹. Earlier communication from these laboratories described the synthesis of new chromone substituted benzopyranopyrimidines 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 work¹⁰. 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 methods¹¹. 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 method¹².



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-Aryl-5-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, $^1\text{H-NMR}$ and Mass spectra. The basic support for the structures of 3 & 5 was provided by $^1\text{H-NMR}$ spectra which prove the presence of building block $-\text{OCH}_2(\text{C-6})-\text{CH}(\text{C-6a})-\text{CH}(\text{C-7})\text{N}$. Thus the $-\text{OCH}_2$ 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} , $\text{C}=\text{O}$ 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, $^1\text{H-NMR}$ 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. $^1\text{H-NMR}$ 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-benzopyrano[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**, $\text{R}_1=\text{H}$, $\text{R}_2=\text{CH}_3$, 3.18 g, 0.01 mole) and 3-(4'-chlorophenyl)-5-aminopyrazole (**2**, $\text{R}_3=\text{Cl}$, 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} ($\text{C}=\text{O}$, chromone) ms (70ev) m/z (%); 494(M^+ , 29%), 346(32%), 307(36%), 207(20%), 154(100%), 137(66%). $^1\text{H-NMR}(\text{CDCl}_3)$: δ 2.5 (s, 3H, CH_3); 3.25(m, 1H, $\text{C}_{6a}\text{-H}$); 4.7(m, 2H, $-\text{OCH}_2$); 5.9(d, 1H, $\text{C}_7\text{-H}$); 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 $\text{C}_{29}\text{H}_{20}\text{ClN}_3\text{O}_3$ 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, R₁=F, R₃=OCH₃, R₄=CH₃)

A mixture of 6-fluoro-3-(4'-methylbenzylidene)-4H-2,3-dihydrobenzopyran-4-one(4, R₁=F, R₄=CH₃, 2.68gm, 0.01 mole) and 3-(4'-methoxyphenyl)-5-aminopyrazole(2, R₃=OCH₃, 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%). ¹H-NMR(CDCl₃): δ 2.4 (s, 3H, CH₃); 3.41(m, 1H, C_{6a}-H); 3.8(s, 3H, OCH₃); 4.15(m, 2H, -OCH₂); 4.8(dd, 1H, C₇-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 C₂₇H₂₂FN₃O₂ requires C, 73.82; H, 5.01, N, 9.56%)

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

References

1. A.R. Katrizky and C.W. Rees, *Comprehensive Heterocyclic Chemistry* 5, 305, 1984.
2. K. Senga, T. Novison and H.R. Wilson, *J. Med. Chem* 24, 610, 1984.
3. M.H. Elnagdi, S.M. Fahmy, E.M. Zayed and M.A.M, Ilias, *Z. Natur for Sch*, 31b, 795, 1976.
4. A. Joseph Schneider, US 4, 666, 916, *Chem. Abstr* 107: 7780 g 1987.
5. A. Karim, M.N. Gohar, F.F.Abdhatiff and MS Eektasty, *Indian. J. Chem*, 25B, 404, 1986.
6. W.J. Irwin and D.G. Wibberley, *J.Chem.Soc. c*, 1745 1967.
7. J. Quiroga, B. Insuasty, A. Sanchez, M.Nogueras and H. Meier, *J. Heterocyclic Chem*, 29, 1045 1992.
8. B. Insuasty, M. Ramos, J. Quiroga, A. Sanchez, M. Noguaras, N. Handd and H. Meier, *J. Heterocyclic Chem*, 31, 61 1994.
9. *Drugs of the future* 21(1), 37, 1996.
10. G. Jagath Reddy, D. Latha, C. Thirupathaiah, K. Srinivasa Rao and Md. Khalilullah, *Heterocyclic Commun* (accepted 2003).
11. K.V. Reddy, G. Sabhitha, A.V.S Rao, *Org. Prep. Proced. Intl* 28(3) 325, 1996.
12. M.H. Elnagdi, S.M. Fahmy, E.A.A Hafez, M.R.H. Elmoghayar and S.A.R Amer, *J. Heterocyclic Chem*, 16, 1109 1979.
13. Representative ¹H-NMR Spectra: 3c (CDCl₃): δ 3.2(m, 1H, C_{6a}-H); 3.8(s, 3H, CH₃); 4.65(m, 2H, C₆-H); 5.85(d, 1H, C₇-H); 7.0-8.0(m, 11H, aromatic and pyrazole) 9.8(s, 1H, chromone). 3g (CDCl₃): δ 2.4(s, 3H, CH₃); 3.25(m, 1H, C_{6a}-H); 4.7(m, 2H, C₆-H); 5.85(d, 1H, C₇-H); 7.0-8.0(m, 11H, aromatic and pyrazole); 9.5(s, 1H, chromone H). 5a (CDCl₃): δ 2.4(s, 3H, CH₃); 3.4(m, 1H, C_{6a}-H); 3.8(s, 3H, OCH₃); 4.17(m, 2H, C₆-H); 4.8(d, 1H, C₇-H); 6.6(s, 1H, Hpyr); 6.8-7.9(m, 11H, aromatic).

Received on June 7, 2003.

