Synthesis of 2-Aryl-4-(1,3-diarylprazol-4-yl)-benzopyrano[4,3-*b*]pyridines

G. Jagath Reddy* 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.Department of

and

Md. Khalilullah, D. Latha and C. Thirupathaiah

Department of Chemistry, Jawaharlal Nehru Technological University, Hyderabad-500 072, India.

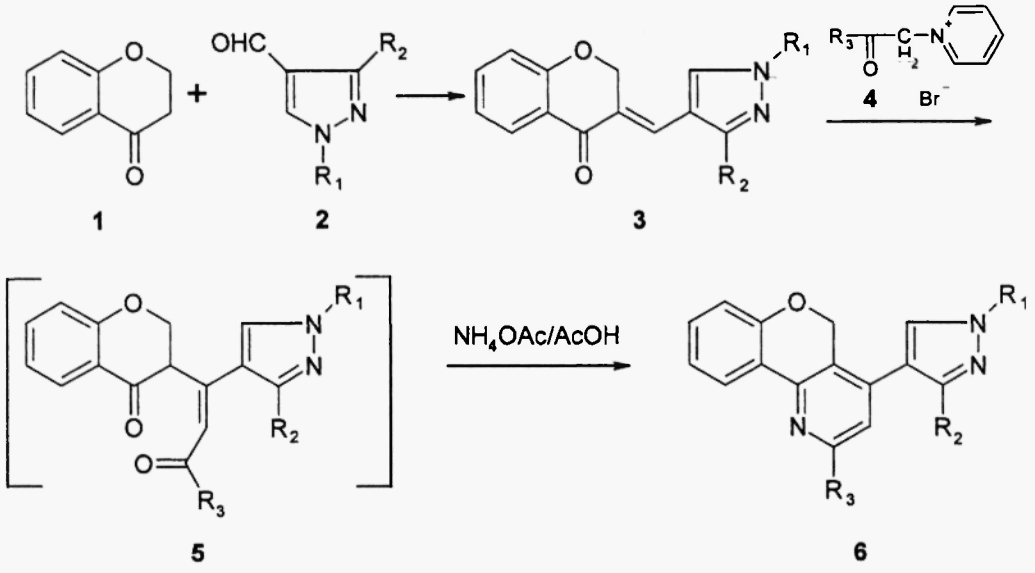
Abstract : A series of 2-aryl-4-(1,3-diarylpyrazol-4-yl)benzopyrano[4,3-*b*]pyridines (6a-h) have been synthesized.

Introduction

The pharmacological properties associated with benzopyrans[1] has created interest in the synthesis of benzopyrano fused heterocycles. Thus several benzopyrano pyridines with anti allergic activities[2] have been reported. Recently this class of compounds have also been reported useful in the treatment of diabetes impaired glaucoma tolerance, ulcerative colitis, Crohn's disease, hypertension and obesity disorders[3]. Furthermore, several pyrazoles are known for their biological activities such as antianxiety[4], antipyretic, analgesic and antiinflammatory[5]. Previous publications from these laboratories has described the synthesis of several benzopyranopyridines substituted with interesting pharmacophores like coumarins[6], chromones[7] and benzoxazines[8]. In continuation of our work on pyrazoles[9], we report herein the synthesis of some new benzopyranopyridines substituted with pyrazoles.

α,β-Unsaturated ketones are useful intermediates for the synthesis of a variety of heterocyclic compounds. Exocyclic α,β-enones in which carbonyl group forms part of the ring system are also useful for the synthesis of various polycyclic ring systems[10]. In the present work, the exocyclic α,β-unsaturated ketone system (**3**) is obtained by the condensation of 2,3-dihydro-4H-benzopyran-4-one (**1**) with substituted 1,3-diarylpyrazole-4-carboxaldehydes **2** in the presence of sodium methoxide in refluxing methanol. **3** Underwent smooth cyclocondensation with phenacyl pyridinim bromides **4** in the presence of ammoniumacetate in refluxing acetic acid to give the desired 4-pyrazolyl benzopyrano pyridines **6** in good yields (Scheme-1). The formation of **5** is evident by the absence of carbonyl function in IR spectra and the shift of $-OCH_2$ signal from δ 5.22 present in **3** to δ 4.82 ppm in the cyclic system in the ^1H NMR spectra of **6** apart from the other aromatic,

pyrazole and pyridine protons. All the compounds reported in Table 1 were characterized by their correct IR, ^{1}H NMR, Mass and elemental analyses.



Scheme-1

The formation of benzopyranopyridines **6** involves the Kröhnke's mechanism[11]. Thus, initial Michael addition of phenacyl pyridinim bromide (**4**) on α,β-unsaturated system gives 1,5-dicarbonyl system **5** which subsequently undergoes cyclization in the presence of NH_4OAc/acetic acid to give **6**.

Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on Perkin Elmer system 2000 FT IR spectrometer in KBr pellets. ^{1}H NMR spectra were recorded on a Varian 200 MHz instrument with TMS as internal standard. Chemical shifts were expressed in δ ppm. Mass spectra were recorded on Hewelett Packard Mass spectrometer operating at 70 eV.

Synthesis of 3-(1,3-diaryl pyrazolomethyl-4-yl)-2,3-dihydro-4H-1-benzopyran-4-one 3: General procedure

To a mixture of 2,3-dihydro-4H-1-benzopyran-4-one (**1**, 0.01 mole) and 1,3-diarylpyrazole-4-carboxaldehyde (**2**, 0.01 mole) in methanol (50 ml) was added sodium (0.02 mole) and stirred under reflux for 2-3 hrs until the disappearance of starting materials as monitored by TLC. The separated solid was filtered and washed with cold methanol to give **3** in pure form.

Table-1 : Physical and spectral data of compounds **3** & **6.**

Compd*	R_1	R_2	R_3	Yield %	M. p °C	Mol. Formula	^{1}H NMR - δ ppm – DMSO-d_6
3a	4-$CH_3C_6H_4$	4-C C_6H_4		68	159	$C_{16}H_{19}ClN_2O_2$	2.37(s, 3H), 5.21(s, 2H), 6.93(d, 1H), 7.12(m, 1H), 7.42(m, 6H), 7.62(m, 2H), 7.77(m, 2H), 7.92(s, 1H), 7.99(d, 1H)
3b	4-FC_6H_4	4-FC_5H_4		71	185	$C_{25}H_{16}F_2N_2O_2$	5.22(s, 2H), 6.91(d, 1H), 7.03(m, 1H), 7.41(m, 6H), 7.61(m, 2H), 7.76(m, 2H), 7.92(s, 1H), 7.98(d, 1H)
3c	3-$CH_3C_5H_4$	4-BrC_6H_4		69	169	$C_{16}H_{15}BrN_2O_2$	2.38(s, 3H), 5.21(s, 2H), 6.94(m, 1H), 7.14(m, 1H), 7.44(m, 6H), 7.63(m, 2H), 7.76(m, 2H), 7.93(s, 1H), 8.01(d, 1H)
3d	2-FC_5H_4	4-$CH_3C_6H_4$		67	191	$C_{16}H_{19}FN_2O_2$	2.39(s, 3H), 5.21(s, 2H), 6.92(d, 1H), 7.19(m, 1H), 7.43(m, 6H), 7.61(m, 2H), 7.76(m, 2H), 7.92(s, 1H), 7.98(d, 1H)
6a	4-$CH_3C_6H_4$	4-ClC_5H_4	C_6H_5	67	212	$C_{31}H_{24}ClN_3O$	2.39(s, 3H), 4.82(s, 2H), 6.81(d, 1H), 7.12(m, 1H), 7.26(m, 5H), 7.42(m, 5H), 7.61(m, 3H), 7.98(s, 1H), 8.13(d, 2H), 8.42(d, 1H)
6b	4-$CH_3C_6H_4$	4-C C_6H_4	4-C C_6H_4	71	217	$C_{34}H_{23}Cl_2N_3O$	2.38(s, 3H), 4.82(s, 2H), 6.83(d, 1H), 7.12(m, 1H), 7.28(m, 4H), 7.41(m, 5H), 7.61(m, 3H), 7.96(s, 1H), 8.12(d, 2H), 8.41(d, 1H)
6c	4-FC_5H_4	4-FC_5H_4	C_5H_5	72	235	$C_{33}H_{21}F_2N_3O$	4.82(s, 2H), 6.81-7.32(m, 9H), 7.53(m, 4H), 7.61(s, 1H), 7.78(m, 1H), 7.96(s, 1H), 8.17(d, 2H), 8.48(d, 1H)
6d	4-FC_5H_4	4-FC_5H_4	4-C C_6H_4	69	241	$C_{33}H_{20}ClF_2N_3O$	4.81(s, 2H), 6.84-7.34(m, 9H), 7.49(m, 3H), 7.63(s, 1H), 7.81(m, 1H), 7.97(s, 1H), 8.21(d, 2H), 8.49(d, 1H)
6e	3-$CH_3C_5H_4$	4-BrC_6H_4	C_5H_5	74	244	$C_{31}H_{21}BrN_3O$	2.41(s, 3H), 4.79(s, 2H), 6.79(m, 1H), 7.13(m, 1H), 7.28(m, 5H), 7.42(m, 5H), 7.63(m, 3H), 7.99(s, 1H), 8.13(d, 2H), 8.41(d, 1H)
6f	3-$CH_3C_6H_4$	4-BrC_6H_4	4-ClC_6H_4	73	209	$C_{34}H_{23}BrClN_3O$	2.38(s, 3H), 4.81(s, 2H), 6.81(m, 1H), 7.12(m, 1H), 7.28(m, 4H), 7.40(m, 5H), 7.62(m, 3H), 7.98(s, 1H), 8.12(d, 2H), 8.42(d, 1H)
6g	2-FC_5H_4	4-$CH_3C_6H_4$	C_6H_5	76	183	$C_{34}H_{24}FN_3O$	2.39(s, 3H), 4.81(s, 2H), 6.81(s, 1H), 7.09(d, 2H), 7.32(m, 5H), 7.41(m, 5H), 7.62(s, 1H), 8.12(d, 2H), 8.19(m, 2H), 8.42(d, 1H)
6h	2-FC_5H_4	4-$CH_3C_6H_4$	4-ClC_6H_4	72	211	$C_{34}H_{23}ClFN_3O$	2.38(s, 3H), 4.82(s, 2H), 6.81(d, 1H), 7.09(d, 2H), 7.32(m, 4H), 7.41(m, 5H), 7.62(s, 1H), 8.09(d, 2H), 8.19(d, 2H), 8.41(d, 1H)

*Satisfactory C, H and N analyses were obtained for all the compounds.

Synthesis of 2-aryl-4-(1,3-diarylpyrazol-4-yl)-benzopyrano[4,3-*b*]pyridines 6: General procedure

A mixture of (**3**, 0.01 mole), phenacylpyridinim bromide (**4**, 0.01 mole) ammonium acetate (0.06 mole) and acetic acid (50 ml) was refluxed for 4-6 hrs. The reaction was monitored by TLC. At the end of the reaction, it was cooled, filtered and the solid was washed with cold water and dried. The products thus obtained were recrystallized from DMF-MeOH to give pure **6** as crystalline solids. Characterization data of all the compounds **6a-h** thus prepared are listed in Table –1.

References

1. J. D. Hapuorth, *Comprehensive Heterocyclic Chemistry*, **3** edited by J.A. Bonlton, A. Mikillap, Pergaman, Oxford 737 (1984).
2. A. Nohara, T. Ishiguro, K. Ukawa, H. Sugihara, Y. Mak, Y. Sanno, *J. Med. Chem.* **28**, 559 (1985).
3. *Drug Data Report* **25**, 720 (2003) edited by JR Prous
4. D. J. Wustrow, T. Capiris, R. Rubin, J. A. Knobelsdory, Akunne, M. O. Davis, R. Mackenzie, T. A. Puysley, K. T. Zoski, T. G. Heffener, L. D. Wise, *Bio org. Med. Chem. Lett.* **8**, 2067 (1998).
5. a) G. Menozzi, L. Mosti, P. Fossa, F. Matholi, M. Ghia, *J. Heterocycl. Chem.* **34**, 963 (1997).
   b) J. D. Penning, J. J. Talley, S. R. Bettenshaw, J. S. Cartour, P. W. Collins, S. Docter, M. J. Graneto, L. F. Lee, J. W. Malecha, J. M. Miyashiro, R. S. Rogers, D. J. Rojers, S. S. Yu, G. D. Anderson, L. G. Burton, J. N. Cogburn, S. A. Gregory, C. M. Koboldt, W. E. Perkins, K. Seibert, A. W. Veenhuizen, Y. Y. Zhang, P. C. Isakson, *J. Med. Chem.* 40, 1347 (1997).
6. G. Jagath Reddy, C. Thirupathaiah, D. Latha, K. Srinivasa Rao, Md. Khalilullah, *Ind. J. Chem.* (2004).
7. G. Jagath Reddy, D. Latha, C. Thirupathaiah, K. Srinivasa Rao, *Heterocycl. Commun.* **10**, 43 (2004).
8. G. Jagath Reddy, D. Latha, C. Thirupathaiah, K. Srinivasa Rao, *Heterocycl. Commun.* **9**, 351 (2003)
9. G. Jagath Reddy, K. Pallavi, R. Shailaja Reddy, K. Srinivasa Rao, *Indian J. Chem.* **43B**, 2702 (2004).
10. A. Levai, *J. Heterocycl. Chem.* **41**, 299 (2004).
11. Kröhnke, *Synthesis*, 1 (1976).

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