SYNTHESIS OF SOME NEW 3-BENZOPYRANOPYRIDINYL AND 3-PYRAZOLYL 1,2-BENZISOXAZOLES FROM *o*-HYDROXYHETEROARYL KETONES DERIVED FROM 3-FORMYLCHROMONE

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Abstract

A series of 3-Benzopyranopyridinyl and pyrazolyl 1,2-benzisoxazoles (**5** & **9**) has been prepared from *o*-hydroxyarylketones (**2** & **6**) derived from 3-formylchromone (**1**).

Introduction

A variety of 3-substituted 1,2-benzisoxazoles have been reported to possess physiological properties such as anticonvulsant[1] and antispasmodic activities[2]. Recently two 3-piperidinyl substituted benzisoxazoles, namely Abaperidone Hydrochloride[3] and Iloperidone[4] have been reported to exhibit promising antipsychotic activities. In addition several pyrazole[5] derivatives and benzopyranopyridines[6] have been reported to posses diverse types of biological activities. Furthermore 3-formylchromone **1** is a very reactive intermediate because of the presence of an unsaturated keto group, a conjugated second carbonyl at C3 and a very reactive centre at C2 which allows michael addition of nucleophile with opening of the γ-pyrone ring. These properties make **1** as a versatile synthon from which a variety of *o*-hydroxyheteroarylketones can be readily obtained. In continuation of our work on 3-formylchromone (**1**) based heterocycles[7] and in view of the biological properties associated with 1,2-benzisoxazoles, pyrazoles and benzo-pyranopyridines we became interested in the synthesis of 3-benzopyranopyridinyl and pyrazolylbenzisoxazoles from the intermediate *o*-hydroxyheteroarylketones readily obtained from 3-formylchromone[8] **1**.

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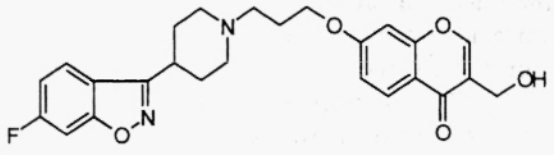

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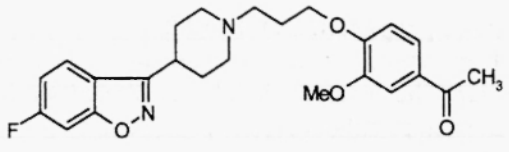
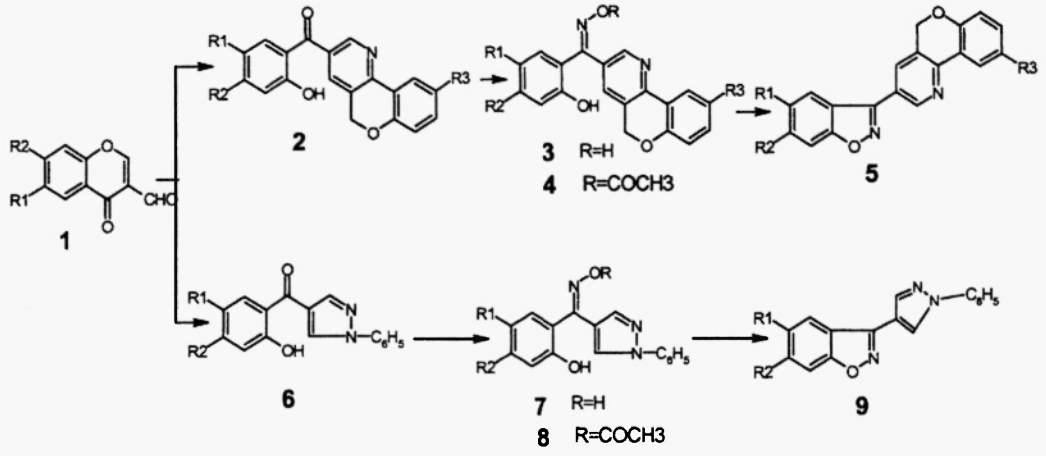


Results and Discussion

The required starting materials 3-(2'-hydroxybenzoyl)-5H(**1**)-benzopyrano(4,3-b) pyridines(**2**) and 4-(2'-hydroxybenzoyl)-pyrazoles (**6**) were readily obtained from 3-formylchromone (**1**). Thus, reaction of chromanone with **1**, gives benzopyranomethyl benzopyranone which on reaction with ammonium acetate in acetic acid or with ammonia in aqueous methonol gives hydroxybenzoylbenzopyrano pyridines[9] (**2a-r**). Reaction of **1** with phenylhydrazine gives

hydroxybenzoylpyrazoles[10] (**6**a-e) in good yields. The corresponding *o*-hydroxyketoximes **3**a-q and **7**a-e were obtained from *o*-hydroxyketones **2**a-r and **6**a-e by refluxing with hydroxylamine hydrochloride in ethanol. The products were characterized by IR and H^1 NMR spectral data. The *o*-hydroxyketoximes **3**a-q and **7**a-f were subjected to cyclization in polyphosphoric acid[11] to give the corresponding 3-heteroaryl 1,2-benzisoxazoles (**5**a-q) and **9**a-e in good yields as crystalline solids. Some ketoximes were also converted to oxime acetates **4** & **8** and they were subjected to intramolecular displacement of acetate from the oxime acetate using sodium hydride in dimethyl formamide[12]. The structures of products have been characterized by analytical data supported by NMR and Mass spectral data (Table 1).



Experimental

General procedure for the preparation of 3 and 7

A mixture of *o*-hydroxyketone (**2** or **6**, 0.07 mole) and hydroxylamine hydrochloride (0.015 mole) in ethanol (15 ml) was refluxed for 6 hrs. The separated solid was filtered washed with water, ethanol and dried to give the products **3** and **7**.

General procedure for the preparation of 5 and 9

A mixture of phosphoricacid (3.4 g) and phosphorous pentoxide (2.5 g) was stirred at 110° for 2 hrs. The ketoximes (**3** or **7**, 0.005 mole) were added to PPA and maintained for 1 hr at 110°. The reaction was monitored by TLC and after completion of the reaction, it was poured onto crushed ice. The separated solid was filtered and washed with water. The crude products were purified by column chromatography using silica gel (ethylacetate : hexane; 1:9) to give pure **5** and **9**.

General procedure for the preparation of 4 and 8.

A mixture of oxime (**3** or **7**, 0.01 mole), acetic anhydride (0.2 mole) was refluxed for 4 hrs. It was poured into ice water. The separated solid was filtered washed with water to give **4** and **8**. They were used in the next step without further purification.

General procedure for the preparation of 5 and 9 via oxime acetates

A mixture of oxime acetate (**4** or **8**, 0.021 mole) was stirred in DMF (10 ml) and NaH (1.1 g, 0.023 ml) at 40° for 4 hrs and poured into H_2O (200 ml). The aqueous solution was extracted with dichloro methane and the extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent gave **5** & **7**.

3-(5H-Benzopyrano [4,3-b] pyridin-3-yl) benz(1,2) isoxazole (5a) ($R_1 = R_2 = R_3$=H)

The *o*-hydroxyketoxime **3**a was converted to **5**a according to the general procedure for the preparation of **5** and **9** to give **5**a (85%) as white crystalline solid. Melting point 216°C, M^+ 300

TABLE-1 PERCENT YIELDS OF CHEMICAL TRANSFORMATION SHOWN IN SCHEME-1

Compound	R_1	R_2	R_3	3[a]	4[a]	5[a]	7[a]	8[a]	9[a]
a	H	H	H	86	-	85	77	-	93
b	CH_3	H	H	78	-	91	81	-	92
c	Cl	H	H	80	-	93	78	-	88
d	Br	H	H	84	-	86	94	-	76
e	F	H	H	79	-	94	95	-	94
f	H	H	CH_3	92	-	77	-	-	-
g	CH_3	H	CH_3	88	-	79	-	-	-
h	Br	H	CH_3	87	-	83	-	-	-
i	F	H	CH_3	96	-	87	-	-	-
j	Cl	CH_3	CH_3	92	-	84	-	-	-
k	CH3	H	Cl	76	-	76	-	-	-
l	H	H	Cl	91	-	94	-	-	-
m	Cl	H	Cl	89	-	93	-	-	-
n	F	H	Cl	86	-	95	-	-	-
o	CH_3	H	F	93	-	88	-	-	-
p	Cl	H	F	95	-	81	-	-	-
q	H	H	F	74	-	86	-	-	-
r	F	H	F	77	-	80	-	-	-

a for melting points see reference, 13

H^1 nmr (200 MHz, DMSO-d_6) : δ 5.40(s, 2H, -OCH_2), 7.00(d, *J*=7.8 Hz, 1H, ArH), 7.15(t, *J*=7.8 Hz, 1H, ArH) 7.30-7.50(m, 3H, ArH), 7.60-7.80(m, 2H, ArH), 8.20-8.35(m, 2H, ArH), 9.4(s, 1H, ArH). Anal. caled. for $C_{19}H_{12}N_2O_2$: c, 76.0%; H, 4.00%; N, 9.33%. found: c, 75.95%; H, 3.92%; N, 9.46%.

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13. Melting points of crystalline products: **3a**, 229°; **3b**, 260°; **3c**, 263°; **3d**, 251°; **3e**, 246°; **3f**, 230°; **3g**, 253°; **3h**, 259°, **3i**, 254°; **3j**, 253°; **3k**, 250°; **3l**, 239°; **3m**, 260°, **3n**, 260°; **3o**, 244°; **3p**, 252°; **3q**, 232°; **3r**, 247°; **5a**, 216°; **5b**, 212°; **5c**, 240°; **5d**, 244°; **5e**, 240°; **5f**, 208°; **5g**, 240°; **5h**, 253°; **5i**, 225°; **5j**, 243°; **5k**, 243°; **5l**, 236°; **5m**, 254°; **5n**, 257°; **5o**, 222°; **5p**, 232°; **5q**, 212°; **5r**, 240°; **7a**, 210°; **7b**, 125°; **7c**, 184°; **7d**, 190°; **7e**, 184°; **9a**, 174°; **9b**, 166°; **9c**, 184°; **9d**, 210°; **9e**, 224°, **4c**, 129°; **4e**, 103°; **8p**, 166°; **8q**, 161°.
14. Representative ^1H nmr spectra: **3g** (DMSO-d_6): δ 2.20(s, 3H, -CH_3), 3.80(brs, Hl), 5.30(s, 2H, OCH_2), 6.65(s, 1H, ArH), 6.9(t, *J*=6.6 Hz, 2H, ArH), 7.00(d, *J*=7.8 Hz, 1H, ArH), 7.20(d, *J*=7.8 Hz, 1H, ArH), 7.60(s, 1H, ArH), 8.10(s, 1H, ArH), 8.5(s, 1H, ArH), 10.4(brs, 1H)

    3p (DMSO-d_6): δ 5.35(s, 2H, -OCH_2), 6.90-7.30(m, 5H, ArH), 7.95(s, 1H, ArH), 8.15-8.35(m, 1H, ArH), 8.65(s, 1H, ArH), 9.15(brs, 1H), 12.00(brs, 1H).

    5g (DMSO-d_6): δ 2.35(s, 3H, -CH_3), 2.45(s, 3H, -CH_3), 5.3(s, 2H, -OCH_2), 6.95(d, *J*=8.1 Hz, 1H, ArH), 7.25(t, *J*=8.1 Hz, 2H, ArH), 7.60-7.75(m, 2H, ArH), 8.00(s, 1H, ArH), 8.45(s, 1H, ArH), 9.30(s, 1H, ArH).

    5p (DMSO-d_6): δ 5.40(s, 2H, -OCH_2), 7.00-7.55(m, 4H, ArH), 8.20(s, 2H, ArH), 8.5(s,1H, ArH), 9.35(s, 1H, ArH).

    7c (DMSO-d_6): δ 6.95(d, *J*=7.8 Hz, 1H, ArH), 7.15-7.55(m, 5H, ArH), 7.70(d, *J*=7.8 Hz, 2H, ArH), 7.90(s, 1H, ArH), 8.50(s, 1H, ArH), 10.85(brs, 1H), 11.45(brs, 1H).

    9b (DMSO-d_6): δ 2.45(s, 3H, -CH_3), 7.25-7.55(m, 6H, ArH), 7.70(d, *J*=8.0 Hz, 2H, ArH), 8.3(s,1H, ArH), 8.6(s, 1H, ArH).

    9e (Dcl_3): δ 7.00-7.10(m, 1H, ArH), 7.30-7.55(m, 5H, ArH), 7.75(d, *J*=7.9 Hz, 2H, ArH), 8.30(s, 1H, ArH), 8.60(s, 1H, ArH).

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