

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

G. Jagath Reddy *, D. Latha, C. Thirupathaiah and K. Srinivasa Rao

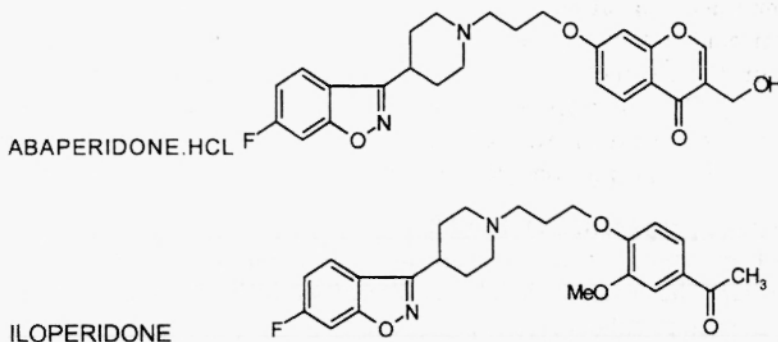
R & D Laboratories, Dr. Jagath Reddy's Heterocyclics, 81, S.V.Co-op Industrial Estate, Balanagar, Hyderabad – 500 037, India. E-mail-jagathreddy@usa.net; Fax #91-40-23773487.

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

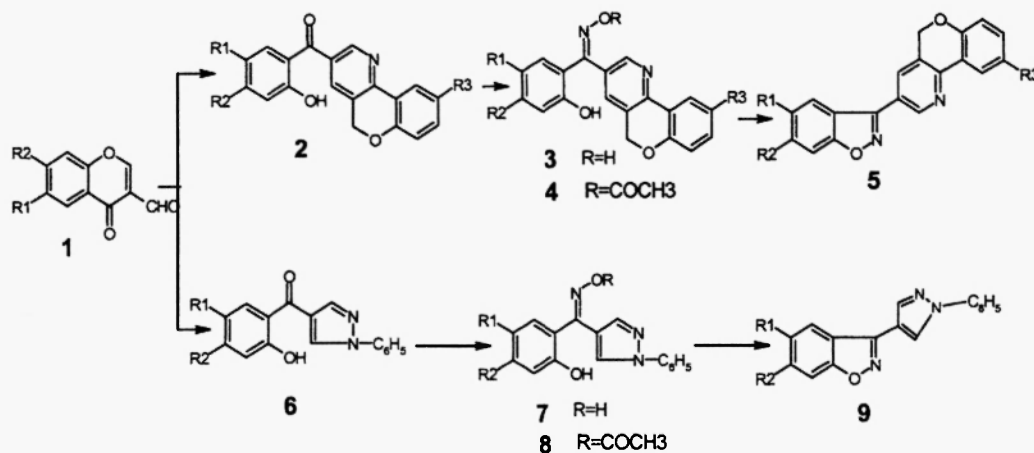
A variety of 3-substituted 1,2-benzisoxazoles have been reported to possess physiological properties such as anticonvulsant¹ and antispasmodic activities². Recently two 3-piperidinyl substituted benzisoxazoles, namely Abaperidone Hydrochloride³ and Iloperidone⁴ have been reported to exhibit promising antipsychotic activities. In addition several pyrazole⁵ derivatives and benzopyranopyridines⁶ have been reported to possess 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 heterocycles⁷ and in view of the biological properties associated with 1,2-benzisoxazoles, pyrazoles and benzopyranopyridines we became interested in the synthesis of 3-benzopyranopyridinyl and pyrazolylbenzisoxazoles from the intermediate *o*-hydroxyheteroarylketones readily obtained from 3-formylchromone⁸ **1**.



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 methanol gives hydroxybenzoylbenzopyrano pyridines⁹ (**2a-r**). Reaction of **1** with phenylhydrazine gives

hydroxybenzoylpyrazoles¹⁰ (6a-e) in good yields. The corresponding *o*-hydroxyketoximes 3a-q and 7a-e were obtained from *o*-hydroxyketones 2a-r and 6a-e by refluxing with hydroxylamine hydrochloride in ethanol. The products were characterized by IR and ¹H NMR spectral data. The *o*-hydroxyketoximes 3a-q and 7a-f were subjected to cyclization in polyphosphoric acid¹¹ to give the corresponding 3-heteroaryl 1,2-benzisoxazoles (5a-q) and 9a-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 formamide¹². 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 phosphoric acid (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 H₂O (200 ml). The aqueous solution was extracted with dichloro methane and the extract was washed with water and dried over Na₂SO₄. Evaporation of the solvent gave 5 & 7.

3-(5H-Benzopyrano [4,3-b] pyridin-3-yl) benz(1,2) isoxazole (5a) (R₁ = R₂ = R₃=H)

The *o*-hydroxyketoxime 3a was converted to 5a according to the general procedure for the preparation of 5 and 9 to give 5a (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	CH ₃	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

^1H nmr (200 MHz, DMSO- d_6) : δ 5.40(s, 2H, -OCH₂), 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. calcd. for C₁₉H₁₂N₂O₂ : c, 76.0%; H, 4.00%; N, 9.33%. found: c, 75.95%; H, 3.92%; N, 9.46%.

References:

1. H. Uno, M. Kurukawa, Y. Masuda and H. Nishimura, *J. Med. Chem.*, 22(2), 180(1979)
2. S. Naruto, H. Mizuta, T. Sawayama, T. Yoshida, H. Uno, K. Kawashima, T. Kadokawa and H. Nishinura, *J. Med. Chem.*, 25, 1240(1982)
3. J.M. Bolos and P.A. Guglietta, *Drugs of the future*, 26(4), 335(2001)
4. J.T. Strupezewski, K.J. Bordeau, V. Chang, E.J. Ggiamkowski, P.G. Convey, R. Corbett, H.B. Hartman, MR. Szewezak, CA willman, G.C. Helsley, *J. Med. Chem* 1119(1985)
5. A.R. Kartritzky, & CW. Ro's *Comprehensive Hetero cyclic chemistry*, 5, 291(1984)
6. A. Nohara, K. Ishigiru, K. Ukawa, H. Sugihara, Y. Maki and Y. Sanno, *J. Med. Chem* 28, 559(1985)
7. G.J. Reddy, G. Sabitha and A.V. Subba Rao, *Synth. Commun.*, 18, 639(1988).
8. G. Sabitha, *Aldrichimica Acta*, 15, 1996
9. K.V. Reddy, G. Sabhitha and A.V. Subba Rao, *Org. Prep. Prced. Int.*, 28(3), 325(1956).
10. C.K. Ghorn and K.K. Mukhopadhyay J. Mohin, *Chem. Soc.* 55, 386(1978)
11. Z.K. Sanmula, K.K. Jurkowski, Ewalichy, K. Bosena, L. Krzywosinki and B. Borkowska, *Pol* 78, 637 *Chem. Abstr* 85: 94347
12. J.T. Strupezewski, R.C. Aven, B.A. Gardner, B.L. Schmid, U. Stache, E.J. Glamkowski, M.C. Janes, D.B. Ellis, F.P. Huger and R.W. Dunn., *J. Med. Chem.*, 28, 761(1985).
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, -CH₃), 3.80(brs, 1H), 5.30(s, 2H, OCH₂), 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, -OCH₂), 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, -CH₃), 2.45(s, 3H, -CH₃), 5.3(s, 2H, -OCH₂), 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, -OCH₂), 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, -CH₃), 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 (DCl₃): 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).

Received on March 21, 2003