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An Unusual Base-mediated Ring Contraction Reaction of Benzopyrans to Benzofurans

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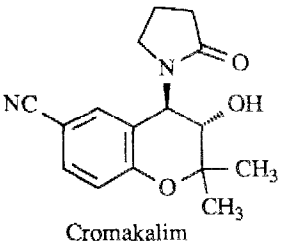
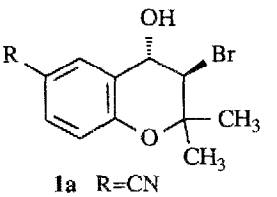
Key Words: benzopyran; benzofuran; ring contraction; pyrrole; cromakalim

Abstract: *The reaction of electron deficient pyrroles and pyrazoles with trans 3-bromo-6-cyano-3,4-dihydro-2,2-dimethyl-2H-1-benzopyran-4-ol under basic conditions results in the formation of 2-isopropylbenzofurans by a mechanism which appears to be dependent on the rate of the competitive dehydration reaction leading to the corresponding benzopyrans.*

The formation of benzothiophenes by the ring contraction of benzothiopyrans is a well recognised phenomenon which, when facilitated by the presence of suitable leaving groups at position 3, may lead to such compounds as the only product class isolated.[1] Benzopyrans, on the other hand, are not known to undergo a similar transformation, possibly because of their inability to form the presumed bicyclo-oxiranium intermediates. Nevertheless, we now report on an unusual ring contraction reaction observed as part of our continued interest in the synthesis of structural analogues of the potassium channel activator, cromakalim.[2,3]



Cromakalim

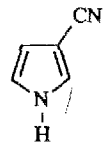
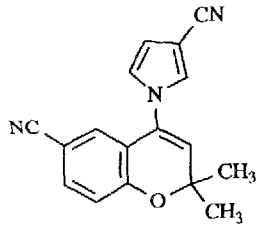
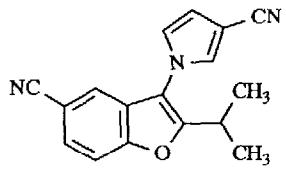
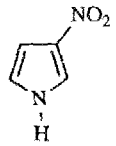
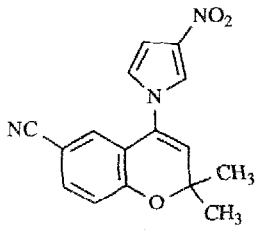
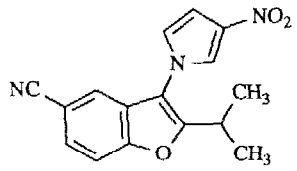
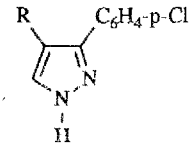
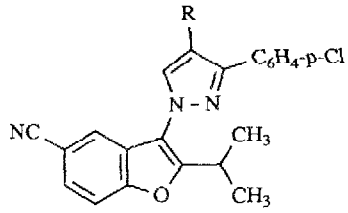
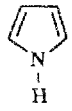
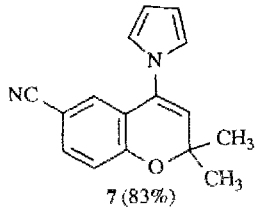
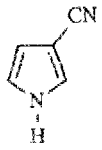
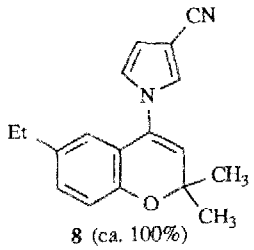


1a R=CN

1b R=Et

(Only relative stereochemistry shown)

Table 1

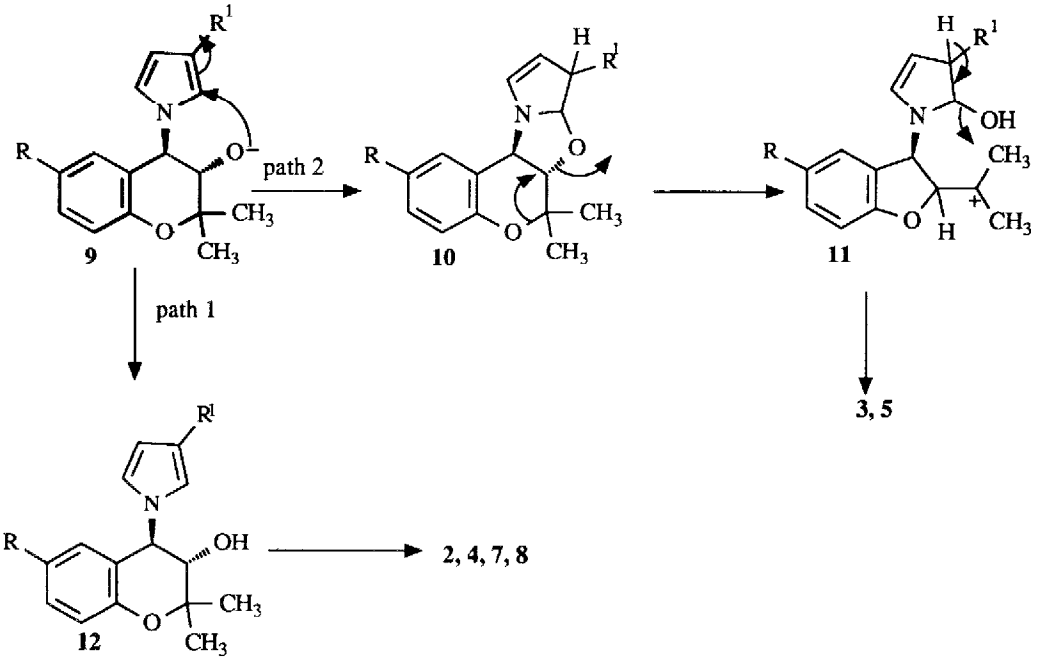
ENTRY NO.	NUCLEOPHILE	PRODUCTS (% YIELDS)	
1		 **2** (23%)	 **3** (38%)
2		 **4** (21%)	 **5** (16%)
3	 (R= p-CH_3-C_6H_4-SO_2)	None	 **6** (40%)
4		 **7** (83%)	None
5		 **8** (ca. 100%)	None

Thus, treatment of the bromohydrin **1a**[4] with the anion derived from 3-cyanopyrrole in N,N-dimethylformamide at 100°C over 20 hours resulted in the formation of two dominant products, the expected benzopyran **2** (23%)* and the 2-isopropylbenzofuran **3** (38%), together with 18% of *trans* 6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-3,4-diol (Table 1, entry 1). A similar reaction of **1a** with 3-nitropyrrole anion also afforded a mixture of the benzopyran **4** (21%) and the benzofuran **5** (16%) (entry 2) accompanied by the *trans* diol. In an analogous fashion, treatment of **1a** with 3-(4-chlorophenyl)-4-(4-methylphenylsulphonyl)pyrazole anion furnished a 40% yield of only the ring contracted product **6** (entry 3) and the above diol. No benzopyran was formed in this instance. In contrast with the 3-nitropyrrole, 2-nitropyrrole failed to add to the bromohydrin **1a** and the addition of magnesium bromide to facilitate the reaction led only to very low yields of 6-cyano-3,4-dihydro-2,2-dimethyl-4-(2-nitropyrrol-1-yl)-2*H*-1-benzopyran- 3-ol. With the anion of pyrrole itself (entry 4) there was no evidence for the formation of the benzofuran on reaction with **1a** and the benzopyran **7** was isolated in high yield. Furthermore, the reaction of 3-cyanopyrrole with the 6-ethylbromohydrin **1b** (entry 5) gave exclusively the benzopyran **8**.

Under these reaction conditions the bromohydrins **1a** and **1b** are rapidly converted into the corresponding epoxides, as shown by earlier studies[4,5] and tlc analysis of the reaction mixtures, and it seems likely that these are converted further into the corresponding alkoxides **9** (Scheme). It is proposed that one of two competitive pathways then ensues. Firstly (path 1), **9** may be protonated leading, via alcohol **12**, to benzopyrans **2, 4, 7** and **8**. Alternatively (path 2), **9** may undergo an intramolecular Michael addition[6,7] leading to the strained *trans*-fused oxazolidine **10**. Collapse of **10** via cleavage of the pyran O1-C2 ether bond followed by dehydration and prototropic rearrangement would give benzofurans **3** and **5**. The Michael addition rationalises the necessity for electron acceptor groups at C-3 of the pyrrole ring (cf entry 1, 2 with 4). Furthermore, it is thought that the electron withdrawing group at C-6 is required (entry 1, 2 and 3) in order to weaken the pyran O1-C2 bond sufficiently to facilitate the migration leading to the collapse of **10**. Without this weakening effect **10** would simply revert to **9** via a retro-Michael reaction and follow path 1 (entry 5). Unfortunately, attempts to convert the independently synthesised alcohol **12** (R=CN, R^1=NO_2)[8] to a mixture of **4** and **5** under conditions approximating to those of the condensation afforded only the dehydrated product **4** (100%). This may be due to the dehydration of **12** being faster than deprotonation of the hindered alcohol to give **9**.

General reaction conditions: 3-Cyanopyrrole (0.46 g, 5 mmol) was added to a solution of *trans*-3-bromo-6-cyano-3,4-dihydro-2,2-dimethyl-2*H*-1-benzopyran-4-ol (1.41 g, 5.0 mmol) and potassium t-butoxide (1.23 g, 11 mmol) in dimethyl formamide (40 ml) and the solution was heated at 100 °C for 20 h. The reaction mixture was cooled, poured into 2M HCl at 0°C and extracted with ethyl acetate. The dried organic phase was evaporated and the residue chromatographed. Elution with 30% EtOAc/hexane gave compound **3** (0.52 g, 38%), m.p. 111-113 °C (Et_2O/hexane), δ ($CDCl_3$) 1.36 (6 H, d, *J* 7 Hz, 2 x CH_3), 3.15 (1 H, heptet, *J* 7 Hz, $CH(CH_3)_2$), 6.68 (1 H, m, 4'-H), 6.84 (1 H, m, 5'-H), 7.31 (1 H, approx t, *J* 1.5 Hz, 6-H), 7.61 (1 H, s, 4-H), 7.62 (1 H, d, *J* 1 Hz, 7-H), 7.68 (1H, m, 2'-H); ^{13}C NMR δ ($CDCl_3$) 20.7 (CH_3), 26.1 (CH_3), 27.8 (CH), 95.3 (q), 107.6 (q), 112.9 (CH), 113.1 (CH), 115.7 (q), 116.0 (q), 118.6 (q), 122.6 (CH), 123.7 (CH), 125.9 (q), 128.5 (CH), 129.1 (CH), 154.0 (q), 160.3 (q) followed by the benzopyran **2** (0.32 g, 23%), m.p. 139-141 °C (EtOAc/hexane), δ ($CDCl_3$) 1.57 (6 H, s, 2 x CH_3), 5.78

(1 H, s, 3-H), 6.61 (1 H, m, 4'-H), 6.77 (1 H, m, 5'-H), 6.97 (1 H, d, *J* 8.5 Hz, 8-H), 7.09 (1 H, m, 2'-H), 7.27 (1 H, d, *J* 2 Hz, 5-H), 7.52 (1 H, dd, *J* 8.5, 2 Hz, 7-H).



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8. Prepared in 16% yield (mp 105-106°C) together with the 2-nitro isomer (18%, mp 121-122°C) by treatment of the corresponding unsubstituted pyrrole with acetyl nitrate.

* All new compounds exhibited satisfactory spectroscopic and microanalytical properties.

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