Tetrahedron Letters, Vol. 34, No. 11, pp. 1815-1818, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

THE SYNTHESIS OF 2,2-BIS(TRIFLUOROMETHYL)BENZOPYRAN DERIVATIVES: A NEW ROUTE TO AN IMPORTANT CLASS OF POTASSIUM CHANNEL ACTIVATORS

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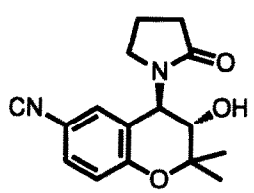
Key Words: Benzopyran; intramolecular cyclisation; potassium channel activator

Abstract: *A new route to an important class of biologically active benzopyrans was developed via an intramolecular cyclisation and cis diol formation.*

Cromakalim 1 and structurally related potassium channel activators are potent smooth muscle relaxants currently under evaluation for the treatment of disorders such as asthma and hypertension[1]. In one attempt to identify an agent with appropriate tissue selectivity we elected to synthesise the 2,2-bis(trifluoromethyl) derivative 2. The trifluoromethyl group at C-6 and the piperidinone moieties at C-4 were used in place of the cyano and pyrrolidone functionalities of cromakalim since earlier SAR studies had identified that such substitutions conferred greater potency to the amidobenzopyranols as relaxants of guinea pig airways.[2]



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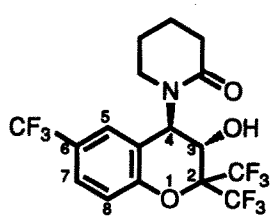
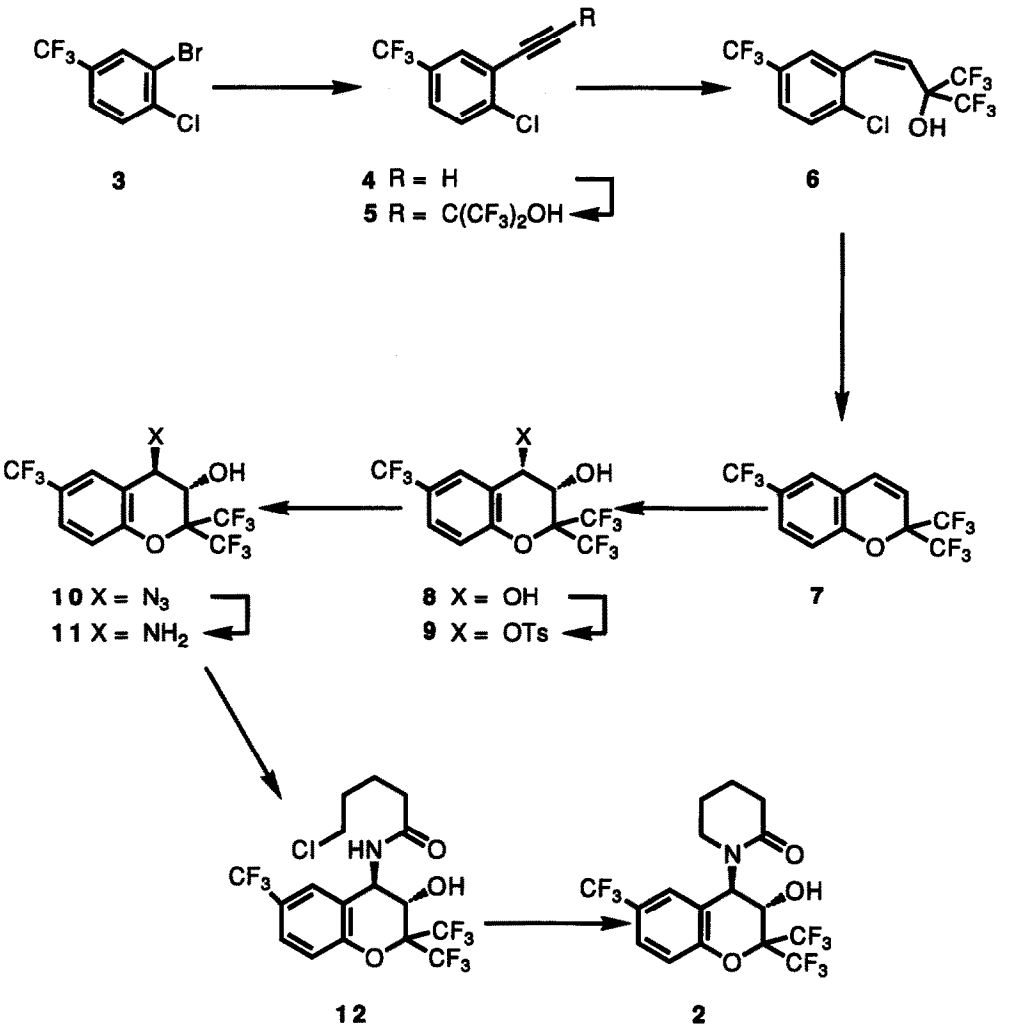


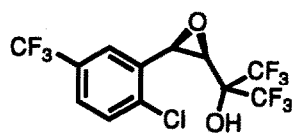
2

The synthesis of cromakalim analogues is normally effected via the corresponding benzopyran.[3] In the case of compound 2 the established synthetic routes would involve substitution at a carbon bearing two trifluoromethyl groups, a process that earlier exploratory reactions had suggested was problematic.[4] An alternative synthesis based on the formation of the pyran ring via an intramolecular nucleophilic displacement of an aryl halide was therefore developed. Such cyclisations are often slow, although it has been shown that complexation of a metal such as chromium to the aromatic ring activates the halogen to displacement.[5] It was felt that the presence of a strong electron withdrawing group would result in similar activation.


CF3
Br
Cl
3
R
4 R = H
5 R = C(CF3)2OH
OH
6
X
7
8 X = OH
9 X = OTs
10 X = N3
11 X = NH2
HN
O
12
2
N

As anticipated from earlier work,[6] the dihalobenzotrifluoride **3**, underwent quantitative and selective replacement of bromide with trimethylsilylacetylene under palladium catalysed coupling conditions [$Pd(PPh_3)_4$, CuI, Et_3N, TMSacetylene, 110°C] yielding the terminal acetylene **4**, after desilylation (K_2CO_3, MeOH, 87%). Introduction of the trifluoromethyl groups was achieved by metallation of the acetylene followed by reaction with hexafluoroacetone [(i) n-BuLi, Et_2O, -78°C, (ii) $(CF_3)_2CO$, -78°C, 91%] giving the alcohol **5**. Partial hydrogenation (H_2, $Pd/BaSO_4$, MeOH/pyridine(20/1), 89%) of **5** afforded the *cis* allylic alcohol **6**, although some isomerization to the trans isomer invariably occurred. The degree of isomerisation was dependent on the time required for hydrogenation of the acetylene, and was typically 5-10%. Finally, deprotonation of the alcohol **6** (NaH, DMSO, 40°C, 79%) resulted in intramolecular cyclisation to give the required benzopyran **7**, in overall 55% yield from the starting halide **3**.

Having prepared the key benzopyran the normal synthesis of cromakalim analogues requires epoxidation of the double bond followed by opening of this with the appropriate amide.[3] Treatment of the pyran **7**, with *m*-chloroperbenzoic acid at 40°C, and at higher temperature, in the presence of the radical inhibitor BHT, gave no epoxide. The more powerful trifluoroperacetic acid similarly failed to oxidise the double bond of **7**. Attempts to carry out the epoxidation of this particularly electron deficient double bond under basic conditions were also unsuccessful. Thus no reaction was observed when the pyran **7**, was treated with hydrogen peroxide in the presence of sodium hydroxide or tetra n-butylammonium fluoride. Finally metal catalysed epoxidation of the double bond with $V(acac)_3$ and t-butyl hydroperoxide was attempted without success. A similar lack of success resulted from attempts to prepare the bromohydrin of **7** as a precursor to the epoxide. The lack of reactivity of the alkene in **7** presumably reflects the electronic and steric effects arising from the adjacent trifluoromethyl groups, a postulate which is supported by the fact that the less hindered acyclic precursor **6** can be oxidised (mcpba, BHT, DCM, 40°C, 59%) to **13**. Unfortunately attempts to cyclise **13** were unsuccessful, with only decomposition products being isolated.



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Oxidation of benzopyran **7** was eventually effected with osmium tetroxide to give the *cis* diol **8**, however due to stable osmate ester formation this reaction would only proceed in the presence of stoichiometric amounts of oxidant (1eq OsO_4, pyridine, 73%). The diol was selectively tosylated on the benzylic hydroxyl group to give the hydroxy ester **9**, (TsCl, pyridine, RT,76%). Displacement of the tosyl group with the anion derived from piperidin-2-one was unsuccessful,

instead causing elimination of the tosyl group via deprotonation at C-3 and demonstrating yet again the powerful electron withdrawing effect of the trifluoromethyl groups. The less basic azide anion gave a good yield of the azido alcohol **10**, (NaN_3, DMSO, 50 °C, 83%) which could be readily reduced (Zn, NH_4Cl, 85%) to the amino alcohol **11**. Acylation of **11** [$Cl(CH_2)_4COCl$, Et_3N, $CHCl_3$, 80%] proceeded as expected to afford the amido alcohol **12**, which readily cyclised (K_2CO_3, KI, refluxing butanone, 57%) to the final product **2**.[7]

The synthesis outlined in this paper offers an alternative to existing routes for the regioselective synthesis of electron deficient benzopyrans and for their elaboration to potassium channel activators. Compound **2** is a potent potassium channel activator *in vitro* which possesses a long duration of action *in vivo*.

Acknowledgements

The help of Dr D.R. Buckle and Dr D.G. Smith in preparing this manuscript and their comments and support during the execution of the work is gratefully acknowledged.

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7)All new compounds were characterised by ^{1}HNMR, IR, Ms & elemental analysis (CHN).

(Received in UK 12 January 1993)