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SYNTHESIS OF THE POTENT POTASSIUM CHANNEL OPENER Ro 31-6930 VIA CLAISEN REARRANGEMENT AND TANDEM REGIOCONTROLLED CYCLISATION

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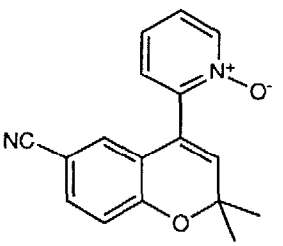
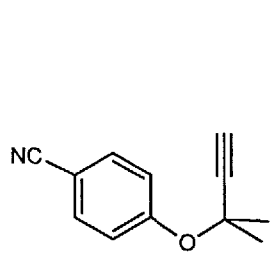
Summary The synthesis of the potent potassium channel opener Ro 31-6930 is reported Methods of controlling the regiochemistry of the crucial cyclisation are described

Potassium channel openers such as cromakalim and pinacidil represent a novel class of smooth muscle relaxants which show promise in a variety of cardiovascular and bronchopulmonary diseases [1] We have recently reported on the rational design[2] and pharmacology[3] of Ro 31-6930 **1** a new member of this class of compounds, and now wish to describe the preparation of this compound using a palladium catalysed coupling of a pyridyl iodide followed by Claisen rearrangement and cyclisation



1

Treatment of the known acetylene **2**[4] with 2-bromopyridine, CuI and triphenylphosphine[5] in diethylamine with a variety of palladium catalysts gave poor yields of the coupled material **3** [6] However when 2-iodopyridine was used with $PdCl_2$ the pyridyl acetylene **3** was obtained in 88% yield When **3** was heated in dichlorobenzene at reflux a mixture of the intended benzopyran **4** and the isomeric benzofuran **5** was formed



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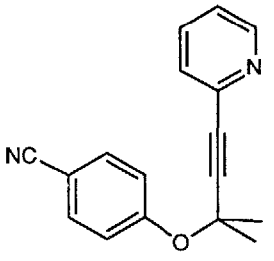

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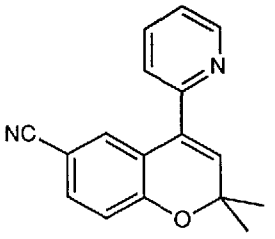

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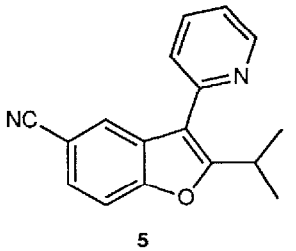


5

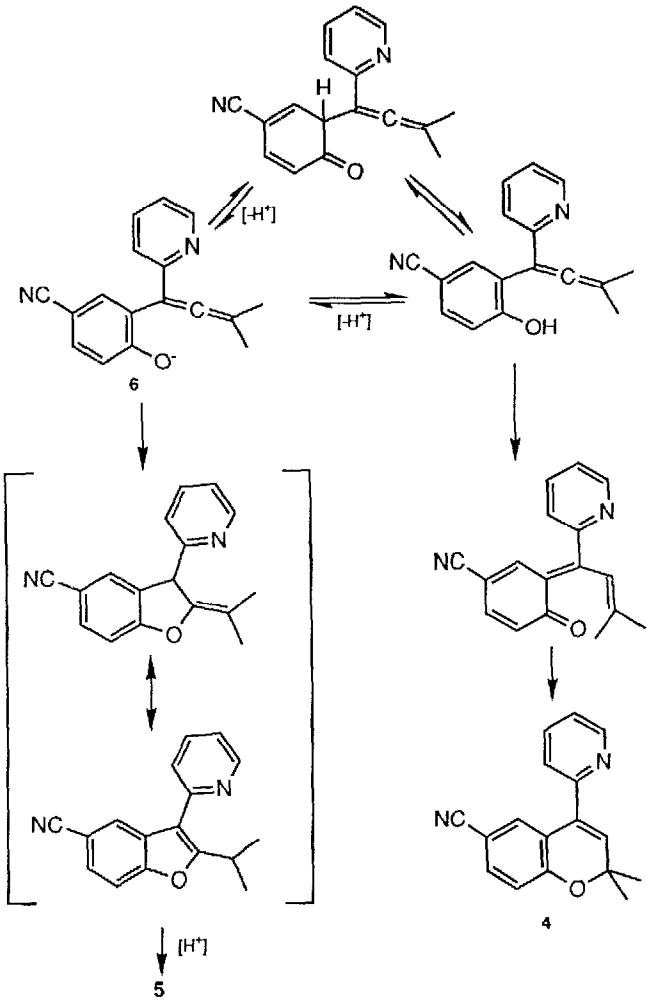
We discovered that higher dilution minimises the formation of **5** Thus a cyclisation carried out at 0 5gml^{-1} in 1,2-dichlorobenzene at 165°C gave isolated yields of 30% and 48% of the benzopyran and benzofuran respectively, whereas at 0 07gml^{-1} under identical conditions 56% benzopyran and 15% benzofuran were isolated Further investigation into the dependence of product ratio on concentration relied upon HPLC determination, the results of which are shown in the table

concentration gml^{-1}	product ratio	
	pyran	furan
0 012	1	0 03
0 021	1	0 06
0 031	1	0 10
0 052	1	0 17
0 099	1	0 40
0 15	1	0 65
0 20	1	0 89
0 30	1	1 11
0 50	1	1 49

Experimental runs for 5 hours at 165°C in 1,2-dichlorobenzene Analysis of products by HPLC SiO_2 25x0 46 cm column 30%v/v ethyl acetate / hexane UV detection 254 nM

The relationship of concentration to product distribution observed implies that in the reaction mechanism a bimolecular step leading to formation of the benzofuran competes with a unimolecular step leading to the benzopyran

The benzopyran presumably forms via the accepted mechanism[7] of 3,3 sigmatropic shift, enolisation, 1,5 hydride shift and cyclisation (see scheme)



SCHEME

Benzofuran products have not been reported from Claisen rearrangements of phenyl propargyl ethers before, although a similar route has been observed for pyrimidinyl propargyl ethers [8] In this case the authors rationalised that the electron withdrawing nature of the pyrimidinyl ring activated the intermediate allene to nucleophilic attack at C_2 promoting cyclisation The conversion of o-allenylphenol to 2-methylbenzofuran has been observed under strongly basic conditions[9] although under milder conditions (triethylamine or thermal) only conversion to the chromene was observed [10] In our case the analogous deprotonation is favoured by the presence of the electron withdrawing group on the aryl ring We believe that the phenoxide **6** will be

favourably disposed to benzofuran cyclisation due to the stabilisation afforded to the resultant anion by the pyridyl group The nature of the base catalysis was investigated with N',N'-dimethyl-4-aminopyridine (DMAP) A reaction at 0 01gml^{-1} with 1 1 mole equivalents of DMAP gave a product ratio of 1 0 12 and with 5 6 mole equivalents of DMAP 1 0 65 compared with 1 0 03 with no additional base, thus demonstrating the increased formation of benzofuran in the presence of a weak base

The high dilution protocol was therefore selected to maximise the yield of the benzopyran To complete the synthesis 4 was oxidised with m-chloroperbenzoic acid in dichloromethane to give Ro 31-6930 in 43% yield together with products resulting from oxidation of the double bond

Thus the highly potent potassium channel opener Ro 31-6930 can be synthesised using this short sequence

References and notes

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6 The authors wish to thank Mr D Brown for carrying out these experiments

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