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The Transformation of a Chromene Derivative into Benzofurans via Allene Intermediates

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Abstract. *On LDA-treatment of chromene* ***1****, allenyl phenol* ***3*** *is formed which recyclizes in solution. Acetate* ***4*** *gives benzofuran derivatives on thermal cyclization.*

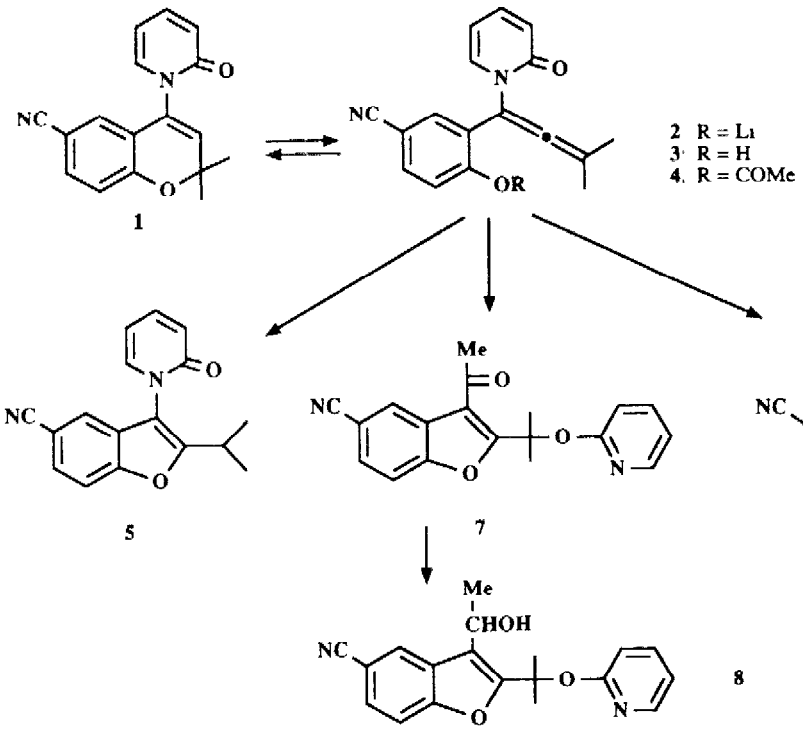
The potassium channel activators represent a new class of pharmacologically active compounds demonstrating high affinity for distinct channels in the membranes of smooth muscle cells.[1] The ability to relax smooth muscle is showing great promise for the treatment of various cardiovascular disorders and asthma. Bimakalim[2] (**1**), which is currently being tested in clinical trials, is a potent K^+ channel activator. Unexpectedly, we obtained an allene derivative in the deprotonation of this chromene compound.

On treatment of the chromene **1** with lithium diisopropylamide in THF at -70 °C and subsequent quenching with a small amount of methanol the allenyl phenol is isolated as lithium salt[3] **2** in good yield. On acidic workup the free allenyl phenol **3**[4] can also be obtained. Both compounds are stable in the solid state.

The preparation of *o*-allenyl phenols starting from chromenes has not been described so far. Nevertheless, Otter et al.[5] could demonstrate spectroscopically the presence of a 6-allenyl-5-hydroxyuracil intermediate in the photochemical rearrangement of a pyrano[3,2-*d*]pyrimidine into a furo[3,2-*d*]pyrimidine. The unsubstituted 2-allenyl phenol is known. It is prepared by Grignard reaction from 2-(chloromethyl)-benzofuran.[6]

3 recyclizes readily to the chromene derivative **1** ($T_{1/2} \approx 20$ min) in chloroform at room temperature. According to HPLC measurements, this process is considerably faster than in the case of the unsubstituted 2-allenyl phenol ($T_{1/2} \approx 18$ h).[6] In the Claisen rearrangement of phenylpropargyl ethers, *o*-allenyl phenols are postulated as intermediates.[5-8] A 1,5-hydride shift followed by cyclization is the proposed mechanism for the final sequence of this rearrangement.

The formation of the allene (**1** → **3**) can formally be considered as a reversal of this sequence. We suppose that initial deprotonation by the strong base at low temperature takes place in position 3. In analogy to the *ortho*-lithiation of aromatic tertiary amides,[9] the pyridone should favor deprotonation in this position. As outlined in **9**, the attacking base (B) opens the ring by E2-elimination and generates the allene. This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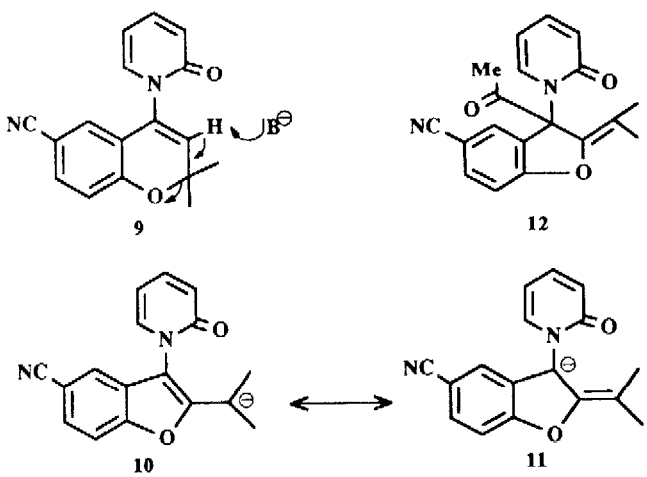
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reaction clearly is assisted both by the presence of a cyano group in the *para*-position which improves the leaving group property of the phenolate and by the final trapping of the open molecule form as the lithium salt **2**

It should be mentioned here, that the course of the reaction with a nucleophilic base is completely different It was reported recently, that methyl lithium adds to **1** in a Michael-type reaction to give a 3-methylchroman compound[10]

The lithium phenolate **2** can be converted into its crystalline acetate **4**,[11] which is achieved by dissolution of the salt in acetic anhydride It has to be stated, that all attempts to prepare the corresponding methyl ether[12] were unsuccessful, probably due to the instability and short half-life of the allene **3** in solution.

On heating in solution, acetate **4** cyclizes to benzofuran derivatives exclusively The observed formation of furan derivatives in a Claisen process by others[5,8] was interpreted as an attack of a phenolate ion on an allene. In our case the thermolysis more probably is started by an attack of the ether-oxygen of the acetate on the allene unit followed by the loss of the acetyl group The nucleophile attacks the C2-position of the allene which is activated by electronegative substituents Depending on the solvents used either resonance form of the possible allyl anion[8] **10** ↔ **11** can be trapped On heating in DMSO at 60 °C for 75 min, the benzofuran compounds **5** and **6**[13] are formed in 27 and 16% isolated yield, respectively The acetyl cation is detached by the aid of DMSO to give an acyloxysulfonium salt[14] and is thus no longer available as electrophile Instead the activated methyl protons of the sulfonium salt serve as a H^+ source to lead to **5** and **6** which are constitutional isomers of bimakalim (**1**).

Formation of a benzofuran of type **5** has already been observed by H Schmid et al in a $AgBF_4$-catalyzed cyclization of 2-allenyl phenol[6] 2-Alkylidene benzofurans were obtained on etherification of phloroglucinol derivatives with propynyl halides[15] We found that compounds **5** and **6** are simultaneously generated and cannot be interconverted under the reaction conditions.

Heating **4** in toluene at 60 °C gives 48% of the benzofuran derivative **7** [16] Structural evidence is (a) an IR band at 1682 cm^{-1} for the conjugated carbonyl group, (b) the missing absorption of a pyridone carbonyl in **7**, and (c) the appearance of a cross-peak between the methyl group and the aromatic H-4 proton in the ROESY spectrum of the reduced compound **8** [17] In the aprotic solvent **7** is formed because the intermediate anion **11** cannot be protonated but captures the acetyl cation (→**12**). Formation of **7** can then be easily explained by a following 3,3-sigmatropic rearrangement of the pyridone The driving force here is a reduction of steric strain in C-3 and the stabilization through resonance on transition of the enol ether entity into a vinylogous carboxylic acid ester.

Of the new compounds allene derivative **4** exhibits potent spasmolytic activity, which is approximately four time less than that of the control **1** [18]

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References and Notes

The article is dedicated to Professor Ekkehard Winterfeldt on the occasion of his 60th birthday.

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3. Lithium 4-cyano-2-[1-(1,2-dihydro-2-oxo-1-pyridyl)-3-methyl-1,2-butadienyl]-phenolate **2**. A solution of bimakalim (**1**, 4.0 g, 14.4 mmol) in dry THF (40 mL) was added dropwise under N_2 at -70 °C to a LDA solution, prepared from diisopropylamine (2.2 mL, 15.7 mmol) and *n*BuLi (9.8 mL, 15.7 mmol, 1.6 M in hexane) in dry THF (40 mL). During the addition, the temperature rose to -60 °C and the solution turned black. After a stirring period of 30 min, MeOH (0.65 mL, 16 mmol) was added dropwise at ambient temperature. The solution faded, and a precipitate was formed. This was collected to give after air drying **2** (2.8 g, 69%) as a pale yellow powder, mp >200 °C dec.

4. 3-[1-(1,2-Dihydro-2-oxo-1-pyridyl)-3-methyl-1,2-butadienyl]-4-hydroxybenzonitrile **3**. Compound **2** (500 mg, 1.76 mmol) was dissolved in 1 N HCl (250 mL) and quickly worked up as follows. After extraction with Et_2O (200 mL), the organic phase was washed with H_2O, dried, and evaporated to yield **3** (80 mg, 16%), mp 123-124 °C, ^{1}H NMR ($CDCl_3$, 253 K) δ 1.85 (s, 6 H), 6.43 (t, J = 6.6 Hz, 1 H), 6.65 (d, J = 9.3 Hz, 1 H), 6.85 (d, J = 8.8 Hz, 1 H), 7.33 - 7.57 (m, 4 H), 10.9 (s br, 1 H).

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11. 4-Acetoxy-3-[1-(1,2-dihydro-2-oxo-1-pyridyl)-3-methyl-1,2-butadienyl]-benzonitrile **4**. Compound **2** (2.65 g, 9.3 mmol) was dissolved in Ac_2O (25 mL) and stirred at room temperature for 90 min. The precipitate formed was collected by filtration and washed with a little Ac_2O to give **4** (2.3 g, 77%) as fine needles with mp >115 °C dec, ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 6 H), 2.10 (s, 3 H), 6.18 (td, J = 7.5, 1 Hz, 1 H), 6.55 (d, J = 9.2 Hz, 1 H), 7.13 (m, 1 H), 7.23 (m, 1 H), 7.35 (td, J = 8.3, 1 Hz, 1 H), 7.55 (m, 2 H).

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13. 2-Isopropyl-3-(1,2-dihydro-2-oxo-1-pyridyl)-benzofuran-5-carbonitrile **5** and 3-(1,2-Dihydro-2-oxo-1-pyridyl)-2,3-dihydro-2-isopropylidenebenzofuran-5-carbonitrile **6**. Compound **4** (2.1 g, 6.56 mmol) was stirred in DMSO (40 mL) at 60 °C for 75 min. After cooling, the reaction mixture was diluted with EtOAc (300 mL) and washed with H_2O (3 × 200 mL). The organic phase was dried and the solvent evaporated. The residue was chromatographed using Et_2O as eluent. From the nonpolar fractions **6** (290 mg, 16%), mp 174-177 °C, and from the polar fractions **5** (490 mg, 27%), mp 122-125 °C, was obtained ^{1}H NMR (DMSO-d_6) of **5**: δ 1.26 (d, J = 6.9 Hz, 3 H), 1.32 (d, J = 6.9 Hz, 3 H), 3.04 (sept, J = 6.9 Hz, 1 H), 6.39 (td, J = 6.7, 1.3 Hz, 1 H), 6.56 (dt, J = 9.3, 0.9 Hz, 1 H), 7.60 (m, J = 9.0, 6.9, 2.0 Hz, 1 H), 7.68 (m, J = 6.9, 2.0, 0.9 Hz, 1 H), 7.78 (dd, J = 8.2, 1.9 Hz, 1 H), 7.64 (d, J = 1.8 Hz, 1 H), 7.67 (dd, J = 8.1, 0.8 Hz, 1 H). ^{1}H NMR ($CDCl_3$) of **6**: δ 1.58 (d, J = 1.5 Hz, 3 H), 1.92 (d, J = 1.9 Hz, 3 H), 6.13 (td, J = 6.8, 1.4 Hz, 1 H), 6.62 (m, J = 9.2, 1.3, 0.8 Hz, 1 H), 7.03 (m, J = 6.9, 2.5, 0.5 Hz, 1 H), 7.06 (d, J = 8.4 Hz, 1 H), 7.27 (m, 1 H), 7.30 (m, J = 8.6, 6.5, 2.0 Hz, 1 H), 7.59 (dd, J = 8.5, 1.7 Hz, 1 H), 7.70 (t, J = 1.1 Hz, 1 H). Structure **6** additionally verified by X-ray diffraction.

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16. 3-Acetyl-2-[1-methyl-1-(2-pyridyloxy)-ethyl]-benzofuran-5-carbonitrile **7**. Compound **4** (900 mg, 2.81 mmol) was warmed in toluene at 60 °C for 5 h. The solution was concentrated and the residue purified on silica gel using EtOAc as solvent to give **7** (430 mg, 48%), mp 112-113 °C, ^{1}H NMR (DMSO-d_6) δ 1.47 (s, 6 H), 2.27 (s, 3 H), 7.10 (d, J = 8.4 Hz, 1 H), 7.17 (m, J = 5.3, 9.0, 0.7 Hz, 1 H), 7.20 (dd, J = 7.2, 0.9 Hz, 1 H), 7.61 (d, J = 1.0 Hz, 1 H), 7.68 (dd, J = 8.3, 1.0 Hz, 1 H), 7.91 (m, J = 9.2, 7.2, 2.0 Hz, 1 H), 8.18 (m, J = 5.0, 2.0, 0.5 Hz, 1 H).

17. 3-(1-Hydroxyethyl)-2-[1-methyl-1-(2-pyridyloxy)-ethyl]-benzofuran-5-carbonitrile **8** was obtained from **7** by $NaBH_4$-reduction: mp 147-149 °C, ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 3 H), 1.43 (d, J = 6.8 Hz, 3 H), 1.53 (s, 3 H), 2.85 (s br, 1 H), 4.91 (q, J = 6.8 Hz, 1 H), 6.91 (d, J = 8.4 Hz, 1 H), 6.96 (d, J = 8.3 Hz, 1 H), 7.05 (m, J = 7.1, 5.0, 0.9 Hz, 1 H), 7.41 (dd, J = 8.3, 2.0 Hz, 1 H), 7.74 (m, J = 8.3, 7.2, 2.0 Hz, 1 H), 8.15 (m, J = 5.0, 2.0, 0.4 Hz, 1 H), 8.25 (d, J = 2.0 Hz, 1 H).

18. Experimental details see reference citation 10. IC_{50}-values: **1** = 0.05 μM, **4** = 0.2 μM, **5** = 3 μM. All the other compounds are only weakly active or inactive. Allenes **2** and **3** were not tested due to instability in solution.

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