Synthesis of 3-(*p*-Halobenzyl)-4-aryl-2*H*-chromenes as Selective Ligands for Antiestrogen-binding Sites

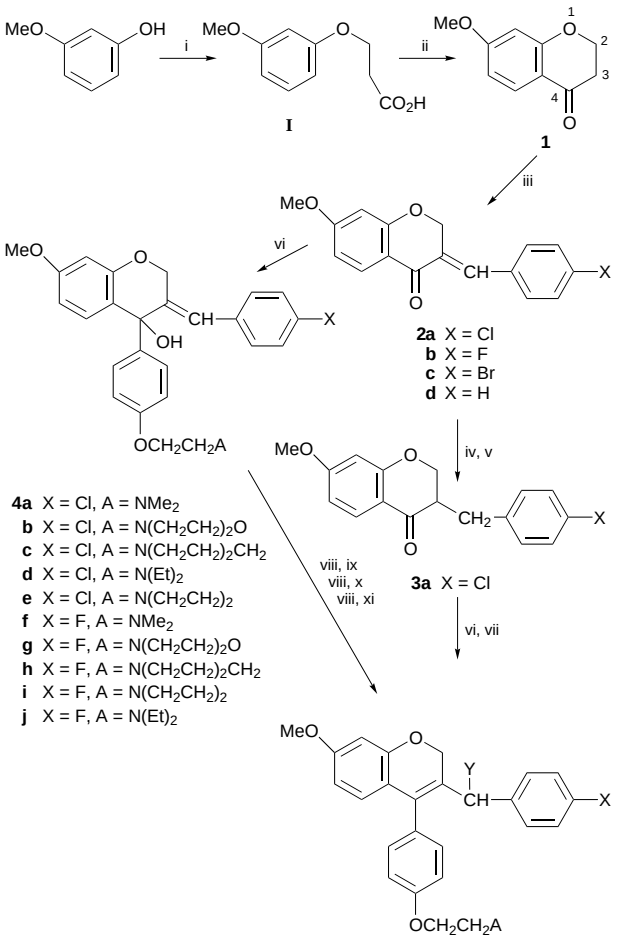
J. Chem. Research (S), 1997, 202–203
J. Chem. Research (M), 1997, 1412–1422

Natarajan Srikanth,[a] Oi-Lian Kon,[b] Siu-Choon Ng[a] and Keng-Yeow Sim*[a]

[a]*Department of Chemistry, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260*
[b]*Department of Biochemistry, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260*

A series of 3-(*p*-halobenzyl)-4-aryl-2*H*-chromenes is prepared in good yields *via* a two-step sequence from the corresponding 3-benzylidenechromanones (homoisoflavanones).

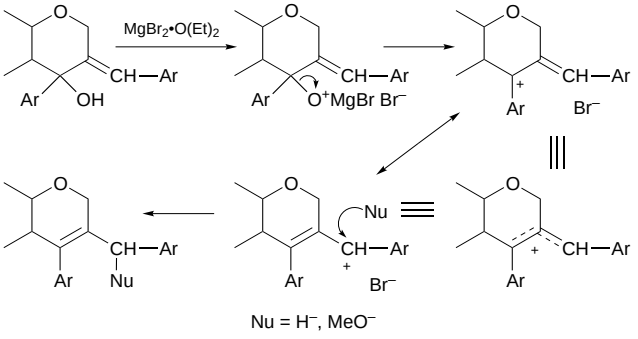
Non-steroidal antiestrogens of triphenylethylene type, principally tamoxifen, have been successfully used in the treatment of hormone-dependent tumours, especially breast cancer.[1,2] Antiestrogens bind to two intracellular proteins, *viz*. the estrogen receptor (ER) and antiestrogen-binding sites (AEBS). Whether AEBS have any role in mediating the non-receptor-dependent inhibition of cellular proliferation is unresolved. We have previously reported the synthesis and biological studies of a series of basic ethers of 3-(*p*-halophenyl)-4-aryl-2*H*-chromenes[3,4] and benzofurans[5,6] which bind to AEBS with equivalent or greater affinity than tamoxifen and display no significant interaction with ER. We report herein the synthesis of a series of basic ethers of 3-(*p*-halobenzyl-4-aryl-2*H*-chromenes derived from 3-benzylidenechromanones as a continuation of a project to prepare non-isomerizable antiestrogens for structure–activity studies which could provide an insight into the functional role of antiestrogen-binding sites.



Scheme 1 *Reagents and conditions:* i, $BrCH_2CH_2COOH$, $NaHCO_3$, NaOH, H_2O, reflux; ii, PPA, 90 °C, 1 h; iii, *p*-XC_6H_4CHO, NaOH, EtOH, r.t.; iv, $NiCl_2{\cdot}6H_2O$, $NaBH_4$, THF, MeOH; v, PCC, CH_2Cl_2, r.t.; vi, *p*-$BrC_6H_4OCH_2CH_2A$, BuLi, THF, −78 °C, aq. NH_4Cl; vii, H^+, MeOH, reflux; viii, $MgBr_2{\cdot}OEt_2$, Et_2O, r.t.; ix, $LiAlH_4$, x, H_2O; xi, MeOH

Based on the methodology used for the synthesis of the title compounds **5a–i** is depicted in Scheme 1. The precursor chromanone **1** was synthesised by treating *m*-methoxyphenol with 3-bromopropionic acid, followed by cyclisation of acid **I** using polyphosphoric acid (PPA).[7] Base catalysed condensation of the desired aldehydes with the chromanone **1**, in the presence of a catalytic amount of sodium hydroxide in refluxing ethanol, afforded the 3-benzylidenechromanones **2a–d** in good yields.[8] Conjugative reduction of the 3-benzylidenechromanone **2a** with sodium borohydride and nickel hexahydrate[9] followed by oxidation with pyridinium chlorochromate (PCC)[10] afforded 3-benzylchromanone (**3a**). Reaction of **3a** with the arylorganolithium reagent followed by acid-catalysed dehydration of the tertiary alcohol afforded **5a** in moderate yield, which might be due to the enolisation of the keto group and subsequent preferential deprotonation of the enol hydroxy moiety. This prompted us to explore an alternative approach of reacting the 3-benzylidenechromanones **2a–d** with the arylorganolithium reagents to give good yields of the allylic alcohols **4a–j** which were transformed into the target compounds **5a–i** by treatment with magnesium bromide etherate followed by lithium aluminium hydride.[6] This interesting transformation must involve an allylic rearrangement, presumably *via* the intermediacy of carbocations, as previously observed for the benzofuran analogues.[6] A possible mechanism for this interesting transformation is illustrated in Scheme 2.

Quenching of the highly coloured magnesium complex (intermediate) with water or methanol yielded the



Scheme 2 Allylic transformation

*To receive any correspondence.

rearranged allylic alcohol **5j** and the corresponding methyl ether **5k**, respectively.

Preliminary screening of compounds **5a–c** in the breast cancer-derived cell line Molt 4 cells indicates that they display similar interesting biological properties as the chromenes[3,4] and benzofurans.[5,6] The results will be reported elsewhere in due course.

We thank the National University of Singapore for a grant in support of this research and for the award of a Research Scholarship to N. S.

Techniques used: IR, ^{1}H NMR, mass spectrometry, elemental analysis, flash and thin layer chromatography

References: 11

Schemes: 2

Table 1: Analytical, physical and spectral data for compounds **1–3**

Table 2: Analytical, physical and spectral data for compounds **4–5**

Received, 24th January 1997; Accepted, 12th March 1997
Paper E/7/00565B

References cited in this synopsis

1 V. C. Jordan, *Pharmacol. Rev*., 1984, **36**, 245.
2 L. J. Lerner and V. C. Jordan, *Cancer Res*., 1990, **50**, 4177.
3 C. C. Teo, O. L. Kon and K. Y. Sim, *J. Chem. Res*, 1990, (*S*) 4; (*M*) 0171.
4 C. C. Teo and K. Y. Sim, *Bull. Singapore Nat. Inst. Chem*., 1994, **22**, 69.
5 C. C. Teo, O. L. Kon, K. Y. Sim and S. C. Ng, *J. Med. Chem*., 1992, **35**, 1330.
6 S. C. Ng, O. L. Kon, K. Y. Sim and N. Srikanth, *Synth. Commun*., 1993, **23**, 1843.
7 P. Perkin, A. Ray and T. Robinson, *J. Chem. Soc*., 1926, 941.
8 P. Pfeiffer, E. Breith and H. Hoyer, *J. Prakt. Chem*., 1931, **237**, 31.
9 D. Dhawan and S. K. Grover, *Synth. Commun*., 1992, **22**, 2405.
10 F. A. Luzzio and W. J. Moore, *J. Org. Chem*., 1993, **58**, 2966.