Synthesis of Chromones by Cyclization of 2-Hydroxyphenyl Ketones with Boron Trifluoride–Diethyl Ether and Methanesulphonyl Chloride

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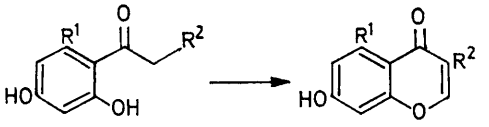
Summary 2-Hydroxyphenyl arylalkyl and alkyl ketones have been cyclised in high yield to the corresponding isoflavones and chromones by treatment with BF_3–Et_2O and $MeSO_2Cl$ in $HCONMe_2$.

ALL chromones, including isoflavones, are theoretically available from the corresponding 2-hydroxyphenyl alkyl ketones *via* the introduction of a one-carbon fragment by *C*-formylation of the ketone. In practice this is not so, and

multi-stage techniques have been developed to enable polyhydroxyisoflavones and chromones to be synthesised.[1,2] A general synthesis of 3-substituted chromones that does not require protection and deprotection stages does not exist. The best previous approach was that of Baker and Ollis *et al.*[1] who used ethoxalyl chloride–pyridine as the cyclisation reagent. Since the methylene function of 2-hydroxyphenyl alkyl ketones is not as activated as in the corresponding aryl analogues (deoxybenzoins), this route does not yield chromones where R^2 is not aryl or heterocyclic.



(I) (II)

I report a single-stage high-yielding synthesis of chromones that is applicable to isoflavones and that does not possess any of the above limitations. A typical procedure is as follows: the 2-hydroxyphenyl ketone (I) in dimethylformamide (DMF) was treated cautiously with BF_3–Et_2O (4 equiv.) when a vigorous exothermic reaction occurred. To this mixture was added a solution of $MeSO_2Cl$ (3 equiv.) in DMF at 50°C. The mixture was heated on a steam bath in an open beaker for 90 min. The cooled product was poured with rapid stirring into water. The initial oil quickly solidified to give the chromone (II) in high purity; it was purified further *via* crystallisation from aqueous ethanol or acetate formation. The Table gives examples of the new procedure.

A sample of biochanin A (IIc) prepared by this route was identical to that prepared by the Baker and Ollis procedure. The 2-hydroxy-ketone precursors (Ia—e) are readily available from the Hoesch reaction[4] of the corresponding nitriles with phenols. BF_3–Et_2O is believed to form a complex with the 2-hydroxy-ketones which deactivates the polysubstituted aromatic ring, thus preventing ring formylation and consequent polymerisation.[5] Simultaneously it activates the methylene function for formylation.

TABLE[a]

(II)	R^1	R^2	Yield (%)	M.p. (*t*/°C)	Ref.
a	OH	*p*-FC_6H_4	98	225—226	3
b	OH	*p*-MeC_6H_4	85	215—217	–
c	OH	*p*-$MeOC_6H_4$	65	211—213	1
d	OH	Ph	82	198—201	3
e	OH	$PhCH_2$	89	177—178	–
f	OH	MeO	66	229—231	–
g	H	cyclo-C_5H_9	60	202—203	–

[a] Satisfactory analytical figures were obtained for all new compounds.

Similar complexes have been proposed to account for the reactivity of 2,2-difluoro-4-methylnaptho-1,3,2-dioxaborin compounds with Vilsmeier reagents.[6] Evidence in support of this mechanism is that 4,6-dimethoxy-2-hydroxyphenyl 3-chlorobenzyl ketone is neither cyclised nor formylated by DMF–$MeSO_2Cl$ alone, but readily affords the corresponding isoflavone in 67% yield in the presence of added BF_3–Et_2O. This new route provides ready access to many polysubstituted naturally occurring isoflavones and hydrogenation of 3-benzylchromones leads to the homoisoflavanone system found in the natural products 3,9-hydroeucomnalin[7] and 3,9-dihydropunctatin.[8]

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