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Novel Methodology for the Synthesis of Estrogenic and Antiestrogenic Isoflav-3-enes

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Abstract: A novel and selective method for the introduction of substituents at the 2-position of the isoflav-3-ene nucleus, utilizing readily available 3-arylcoumarins as starting materials, is described. Thus, addition of a Grignard reagent to the corresponding phenyl acetal provided the desired 2-alkyl-, alkenyl-, or arylisoflav-3-enes. These compounds interact strongly with the estrogen receptor and show estrogenic or antiestrogenic effects depending upon the nature of the 2-substituent.

Isoflav-3-enes (Figure I) have long been recognized as potent synthetic estrogens, with their level of activity dependent upon the presence of phenolic hydroxyl moieties and the nature of substituents R^1, R^2, and R^3.[1-4] Recently, a number of analogs containing amino functionality within the 2-substituent (e.g. **1**) have been prepared and have demonstrated significant antiestrogenic activity.[5,6] They have been shown to bind strongly to the estrogen receptor and inhibit the proliferation of breast tumor cell lines (ZR-75-1)[6] *in vitro*, and to inhibit the *in vivo* effects of estrogen on the mouse uterus with little or no agonist activity.[5] Furthermore, in contrast to other known "pure" antiestrogens,[7] we have demonstrated that some of these derivatives (i.e. **1**) function as Selective Estrogen Receptor Modulators (SERM's), with positive effects on serum lipid and bone parameters.[8]

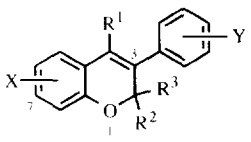
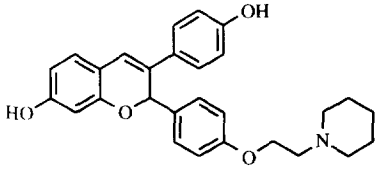


Figure I



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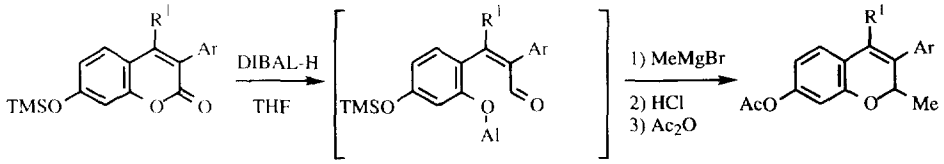
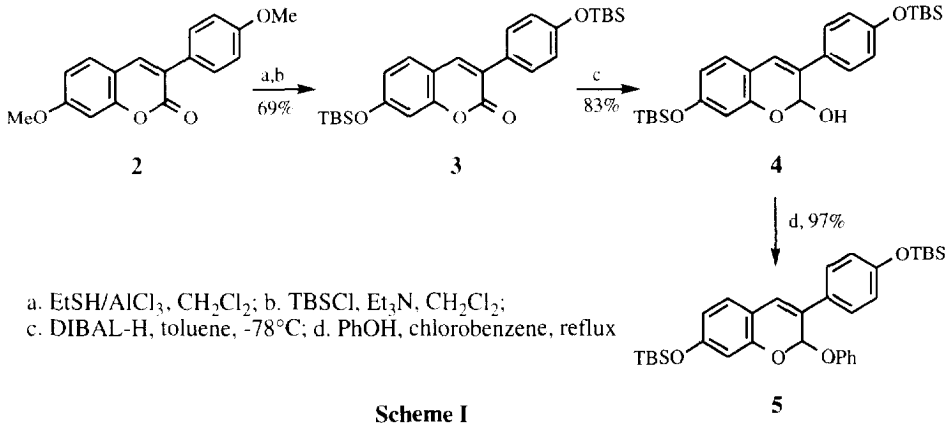


Equation 1

Several groups have previously taken advantage of the ready availability of 3-arylcoumarins as starting materials for the preparation of substituted isoflav-3-enes.[9-12] These methods however, have generally been non-selective and have not been applicable to the preparation of 2-monosubstituted-4-unsubstituted analogs. Furthermore, the relative instability of the phenolic isoflav-3-enes has frequently resulted in the preparation of "protected" versions, which were unstable to the conditions required for their deprotection.

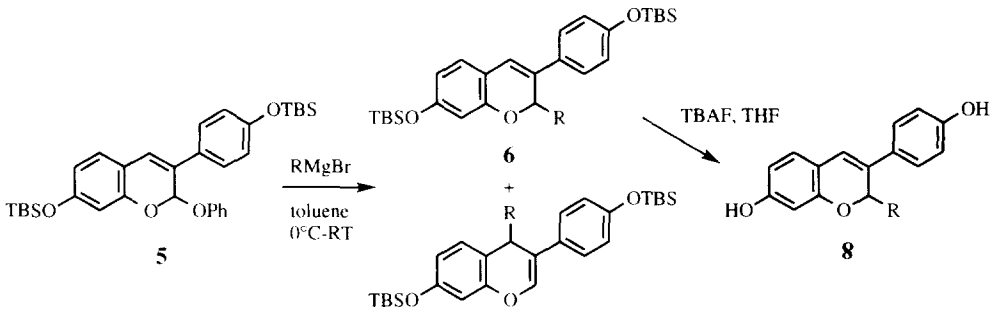
Cook[9] has previously demonstrated that DIBAL-H reduction of an appropriate arylcoumarin, followed by *in situ* reaction with a Grignard reagent and acid-catalyzed cyclization, provided access to 2,4-dialkyl-3-arylisoflav-3-enes (Equation 1). Other researchers however, have reported low yields when a 4-substituent was not present.[11] We ascribed this difficulty to a lack of selectivity in the addition of the Grignard reagent to the intermediate α,β-unsaturated aldehyde and sought to improve the selectivity by isolation of the corresponding lactol, and conversion of the lactol hydroxy into a more reactive leaving group. Furthermore, we reasoned that by capping the lactol hydroxy we would prevent the intermediacy of the aldehyde congener thereby obviating the necessity of a subsequent cyclization under strong acid conditions. Finally, we felt that the preparation of a stable acetal or acetal-like precursor, which could undergo displacement by a suitable organometallic reagent, would provide an advantage with respect to the ease of synthesis of a series of 2-substituted analogs. Herein we report the successful utilization of the corresponding phenyl acetal as a convenient intermediate in the preparation of a variety of biologically active 2-aryl, 2-alkyl, and 2-alkenylisoflav-3-enes.



Scheme I

In order to allow for eventual deprotection of the phenolic isoflav-3-enes, readily available 4',7-dimethoxy-3-phenylcoumarin **2**[13] was demethylated and silylated.(Scheme I) Reduction with DIBAL-H in toluene provided the corresponding lactol **4** in 83% yield, with only trace amounts of overreduced diol and unreacted starting material. Attempted conversion of **4** to the acetate or the methylcarbonate resulted in decomposition. Conversion to the methyl acetal with methanol and catalytic *p*-toluenesulfonic acid was straightforward, however attempted reaction of the methyl acetal with a variety of nucleophiles in the presence or absence of Lewis acids gave unpromising results. Based upon Mukaiyama's precedent involving the reaction of chlorophenyl acetals with Grignard reagents,[14] we attempted to prepare the corresponding phenyl acetal. Simply mixing the lactol with excess phenol in methylene chloride or chlorobenzene provided the requisite acetal **5** in 97% yield. The acetal was unstable to chromatographic purification, but could be stored at 5°C for extended periods without substantial decomposition.

Reaction of this acetal with various Grignard reagents provided the desired 2-substituted isoflav-3-enes **6** in good yields.(Scheme II, Table I) Aryl and vinyl Grignards add with excellent 1,2-selectivity, with only trace amounts of the 4-substituted products **7** detected. For alkyl Grignard reagents, the 1,2-selectivity appears to decline with increasing steric bulk, from essentially complete selectivity for the 1,2-product with methyl



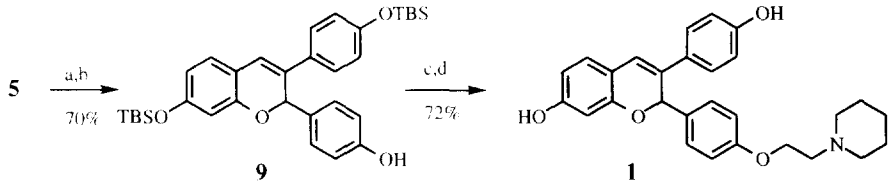
Scheme II

Table I

	R	Yield 6[‡]	Yield 7[‡]	6:7[*]	Yield 8[†]
a	Methyl	84%	---	>95:5	100%
b	Ethyl	37%	34%	1:1	100%
c	Isopropyl	18%	29%	1.5:1	88%
d	Phenyl	86%	---	>95:5	100%
e	4-Fluorophenyl	77%	---	>95:5	100%
f	4-Anisyl	88%	---	>95:5	100%
g	1-Naphthyl	70%	---	>95:5	100%
h	2-Thienyl	84%	---	>95:5	86%
i	Vinyl	82%	---	>95:5	100%

[‡]Isolated yields.
[*]Ratio based on crude ^{1}H-NMR.

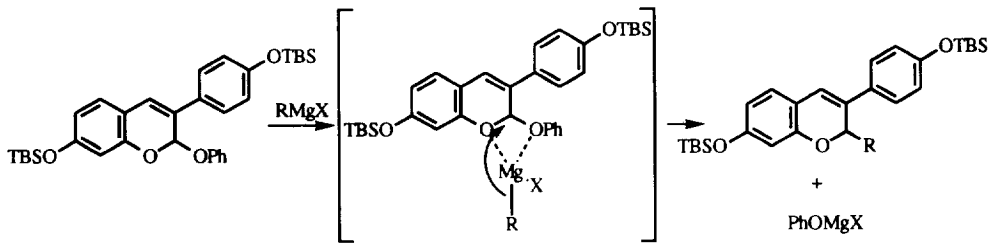
Grignard to approximately 1.5:1 selectivity in favor of the 1,4-product with isopropyl Grignard. Desilylation with tetra-*N*-butylammonium fluoride then proceeds in essentially quantitative yield to provide the desired phenolic isoflav-3-enes **8**. For elaboration to analogs with amino functionality in the 2-substituent, 4-(trimethylsilyoxy)phenylmagenesium bromide[15] can be added and selectively deprotected in 70% overall yield.(Scheme III) Mitsunobu alkylation followed by desilylation then provides the potent SERM **1**.



a. 4-(trimethylsilyloxy)phenylmagnesium bromide, toluene; b. K_2CO_3, MeOH, ether;
c. 1-(2-hydroxyethyl)piperidine, PPh_3, DEAD, toluene; d. TBAF, THF;

Scheme III

Mechanistically, the displacement reaction is believed to proceed as depicted in Equation 2. Thus, magnesium promotes the substitution via coordination with the departing phenoxy moiety, as postulated by Mukaiyama.[14] The failure of acetal **5** to react with organolithium reagents substantiates this hypothesis and



Equation 2

demonstrates the requirement for a more strongly coordinating organometallic species. While the intermediacy of a free oxonium ion cannot be ruled out, the fact that the displacement occurs more readily in toluene (0°C) than in THF (reflux) argues against an ionic intermediate. Furthermore, the addition of excess Lewis acid ($MgBr_2$) led to a decreased ratio of 1,2-product (**6**) to 1,4-product (**7**), implying that under these more strongly ionizing conditions an intermediate oxonium ion might be responsible for the reduced selectivity. Whether increased oxonium ion character in the intermediate is also responsible for the decreased selectivity with alkyl Grignard reagents is not clear.

The 2-substituted isoflav-3-enes[16] show good binding to the estrogen receptor, (binding affinity 1.7-23% relative to 17β-estradiol) with larger (i.e. naphthyl) 2-substituents showing somewhat reduced binding. They are strong inducers of proliferation in an MCF-7 breast tumor cell line, a classical estrogenic response. Conversely, **1** is a strong inhibitor of estrogen-induced proliferation in this cell line (IC^{50} = 0.1 nM), demonstrating the important role of the 2-substituent in controlling biological activity.

In summary, we have developed improved methodology for the installation of 2-substituents onto the isoflav-3-ene nucleus, using readily available 3-arylcoumarins as starting materials. Further modification of various 2-substituents may produce alternative SERM's with improved pharmacological properties and utility in the treatment of a host of estrogen-related diseases including breast cancer, endometriosis, uterine fibroids, osteoporosis, and hyperlipidemia.

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16. All new compounds exhibited appropriate 1H-NMR, 13C-NMR, IR, MS and/or elemental analysis.

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