A Facile Approach to 2-Substituted Isoflav-3-enes via Isoflavylium Salts

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Received 4 September 2008

Abstract: A compact and regioselective approach to 2-substituted isoflav-3-enes based on a preformed 2-unsubstituted isoflavene is described. Isoflavene oxidation by hydride ion abstraction to the corresponding isoflavylium salt using trityl hexafluorophosphate followed by nucleophilic addition to the 2-position resulted in the introduction of a range of substituent groups in generally moderate to good yields.

Key words: nucleophilic additions, isoflavonoid, isoflavylium, isoflavene, trityl salts

Isoflavonoids have gained increasing attention in recent years because of the range of biological activities they display. These activities include estrogen-receptor antagonism,[1a] anticancer (protein kinase inhibition),[1b] antiplatelet aggregation,[1c] anti-inflammatory,[1c,d] antiallergy,[1c] antifungal,[1e] peroxisome proliferator-activated receptor binding,[1f] and diuretic properties.[1g] Isoflav-3-ene (**1a**) (haginin E,[2a] dehydroequol, phenoxodiol), is of great interest as it has been shown to possess significant anticancer activity.[2b] Additionally, **1a** acts as a chemosensitizer to current cancer therapies.[2c]

As part of a general SAR program with compounds of type **1**, we were interested in developing a facile and flexible route to 2-substituted derivatives based on the isoflav-3-ene derivatives **1a–c** (Figure 1).

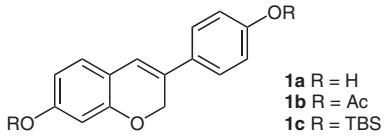
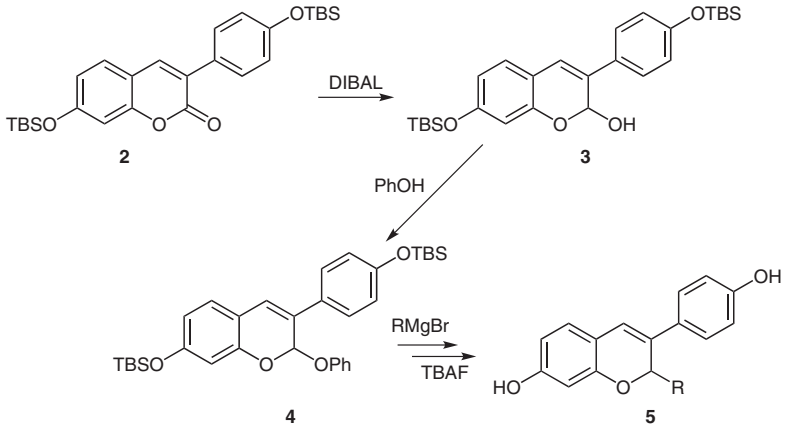


Figure 1 The structure of dehydroequol **1a**, together with the protected analogues **1b** and **1c**

Previous approaches to 2-substituted isoflav-3-enes have included a number based on 3-arylcoumarins. For example,[3] DIBAL reduction of the protected 3-arylcoumarin **2** gave the hemiacetal **3**, which on reaction with phenol afforded the 2-substituted isoflav-3-ene **4** in high yield; reaction of **4** with various Grignard reagents, which in most cases gave the 1,2-product over the 1,4-product, followed by desilylation provided access to **5** (Scheme 1). It was proposed that displacement with the Grignard reagent proceeded via a magnesium-coordinated intermediate rather than a free oxonium ion (isoflavylium ion) intermediate.

In a somewhat similar way, Cook and co-workers accessed 2,4-disubstituted isoflav-3-enes[4a] from 4-substituted 3-arylcoumarins but in this case the Grignard reagent was added to the DIBAL-H reduction product in situ; acid-catalyzed cyclization then gave the isoflavenes. Direct Grignard addition to coumarins results in 2,2-disubstituted analogues.[4b,c]



Scheme 1 A coumarin-based route to 2-substituted isoflav-3-enes[3]

SYNLETT 2009, No. 2, pp 0306–0309
Advanced online publication: 15.01.2009
DOI: 10.1055/s-0028-1087523; Art ID: D31908ST

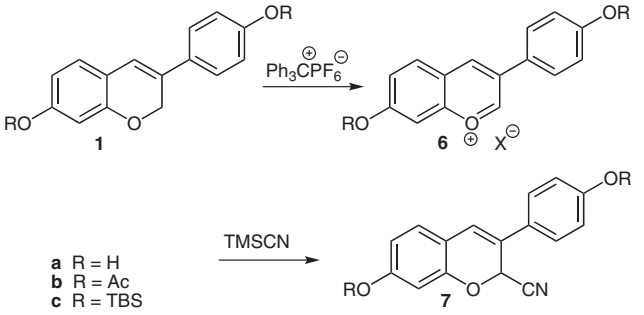
Isoflavones can also serve as precursors for unsymmetrically substituted 2,4-dialkylisoflav-3-enes via sequential reaction with an alkyl lithium followed by a trialkylaluminum reagent.[5]

In a quite different strategic approach, 2-amino substituted isoflav-3-enes have been prepared through microwave-assisted assembly of the substituted pyran ring from substituted *o*-hydroxybenzaldehydes and enamine precursors, and a subsequent Knoevenagel reaction;[6] 2-arylisoflav-3-enes have been prepared similarly from a trihydroxydeoxybenzoin precursor.[7]

Explicit production of an isoflavylium salt precursor for further 2-substituted isoflav-3-ene formation is an alternative and potentially more versatile route, which we have explored. In particular, we investigated direct formation of such salts by hydride ion removal from readily available 2-unsubstituted isoflav-3-ene precursors using trityl salts[8] and then nucleophilic addition to the 2-position. The results are now reported in this paper.

A number of trityl salts was investigated for the hydride abstraction step using the phenol-protected isoflav-3-ene derivatives **1b** and **1c**. These derivatives were formed in turn from **1a**[9a,b] using acetic anhydride and pyridine, or TBS chloride in the presence of imidazole, respectively.

Table 1 Synthesis of Isoflav-3-enes **7**

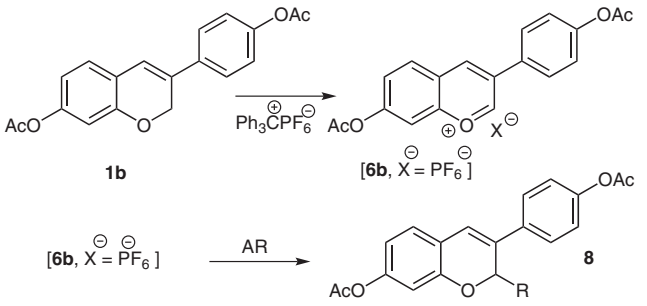


Entry	Isoflavylium ion **6b**,**c**	Counterion (X^-)	Yield of **7b**,**c** (%)
1	**6b**	BF_4^-	43
2	**6b**	$SnCl_5^-$	76
3	**6b**	PF_6^-	80
4	**6c**	PF_6^-	0

With the protected isoflavenes in hand, reaction optimization was explored utilizing TMS cyanide as the nucleophile source for attack on the salts **6b** and **6c** (Table 1).[10] Such nucleophilic addition with TMS cyanide (and other nucleophiles) to related 1-benzopyrylium salts had been demonstrated previously,[11] but these salts were derived from a 2-substituted acetal precursor on treatment with $BF_3{\cdot}OEt_2$. With **1b**, the best yields of **7b** were obtained with the hexafluorophosphate and pentachlorostannate trityl salts, while **1c** failed to give any of the desired product **7c** with trityl hexafluorophosphate salt presumably due to desilylation of the phenolic silyl ether groups by PF_6^- anion acting as a source of fluoride.[12] In view of these results, and taking into account environmental issues associated with the stannate salt, trityl hexafluorophosphate and **1b** were subsequently used to explore the generality of the addition reactions of the isoflavylium salt intermediate.

Various nucleophiles could be added via C–C and C–O bond formation to the 2-position of the salt generated in situ (Table 2).[13] With the C–C bond formation, TMS- or tin-based reagents were used to deliver the nucleophilic component in good to modest yields. Alcohols could also be added readily, as expected, to give the 2-alkoxy derivatives. The structures of the products were confirmed through NMR spectroscopy, and high-resolution mass spectrometry data or elemental analytical data were consistent with the molecular formulae.[14] The regioselectivity of nucleophilic attack at the 2-position over the 4-position in the salt was confirmed by HMBC analysis with a key correlation being observed between a vinylic H4 and C5. This regioselectivity is consistent with the greater double-bond stabilization possible with a stilbenyl moiety compared to the styryl moiety, which would be present from 4-substitution.

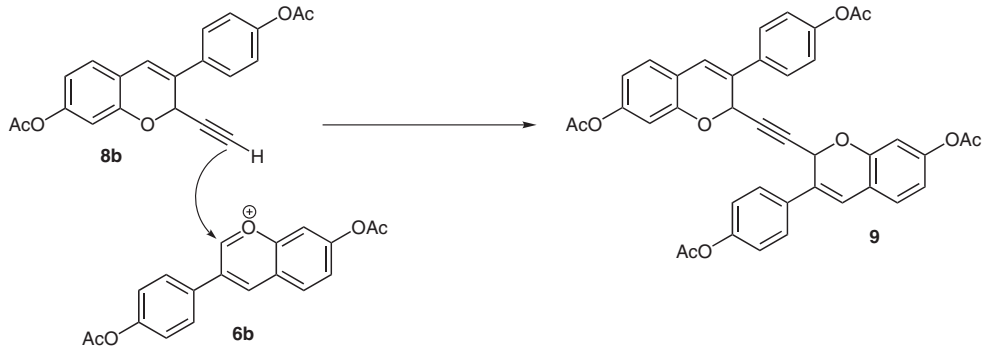
Table 2 Synthesis of the Isoflav-3-enes **8**



Entry	AR	Compound R	Yield (%) of **8a**–**g**
1	2-TMS-thiazole	**8a** 2-thiazolyl	76
2	TMSC≡CH	**8b** C≡CH	7
3	$TMSCH_2N(Boc)_2$	**8c** CH_2NHBoc	45
4	$(Bu)_3SnCH_2CH{=}CH_2$	**8d** $CH_2CH{=}CH_2$	68
5	MeOH	**8e** OMe	63
6	EtOH	**8f** OEt	63
7	$HOCH_2CH_2CH_2Br$	**8g** $OCH_2CH_2CH_2Br$	66

The poor yield of the ethynyl isoflav-3-ene **8b** was due to the formation of the dimeric product **9**, which was isolated in 67% yield. This dimer could arise from fluoride-mediated ethynyl group addition to the isoflavylium ion (Scheme 2).

In conclusion, a new and concise one-pot procedure has been developed for the synthesis of 2-substituted isoflav-3-enes from a readily available isoflav-3-ene precursor utilizing in situ generation of an isoflavylium salt interme-



Scheme 2 Proposed mechanism for the formation of the dimeric product **9**

diate. This is a flexible approach, which allows for the ready introduction of a range of synthetically versatile substituents in this heterocyclic system.

Acknowledgment

J.B.B. thanks the University of Wollongong and Novogen Ltd for financial contribution to the project. A University of Wollongong-Novogen scholarship to J.F. is also gratefully acknowledged.

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(8) (a) Trityl perchlorate has been used previously to access chromylium salts from the dihydro precursors[8b] but not, as far as we can ascertain, from 2-unsubstituted isoflav-3-enes. Isoflavylium salts can also be made, for example, by ring construction[8c] or by trityl salt mediated elimination of 2-substituted isoflav-3-enes[8d] (b) Canalini, G.; Degani, I.; Fochi, R.; Spunta, G. *Ann. Chim. (Rome)* **1967**, *57*, 1045. (c) Bouvier, P.; Andrieux, J.; Molho, D. *Tetrahedron Lett.* **1974**, 1033. (d) Dean, F. M.; Varma, R. S. *J. Chem. Soc., Perkin Trans. 1* **1982**, 1193.

(9) (a) Compound **1a** is accessible from the commercially available precursors daidzein[9c] or daidzein diacetate[9d,e] (b) Faragalla, J. E. *PhD Thesis*; University of Wollongong: Australia, **2005**. (c) Heaton, A.; Jeoffreys, G. WO 2005103025, **2005**; *Chem. Abstr.* **2005**, *143*, 422198. (d) Heaton, A.; Kumar, N. WO 2000049009, **2000**; *Chem. Abstr.* **2000**, *133*, 177059. (e) Liepa, A. J. *Aust. J. Chem.* **1981**, *34*, 2647.

(10) **General Procedure (Table 1, Entry 3)**
A mixture of powdered 3 Å MS, trityl hexafluorophosphate (2.2 mmol), and the isoflavene **1b** (503 mg, 1.55 mmol) in freshly distilled, anhyd CH_2Cl_2 (50 mL, from CaH_2) was stirred at r.t. under nitrogen for 30 min. Trimethylsilyl cyanide (0.480 g, 4.8 mmol) was then added, and the reaction mixture was stirred for a further hour at r.t. The reaction mixture was then filtered, washed with CH_2Cl_2, concentrated under vacuum filtration, and subjected to silica gel chromatography, using CH_2Cl_2 as the mobile phase to afford the product as a colorless crystalline solid (431 mg, 80%).

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(13) **General Procedure (Table 2, Entry 1)**
A mixture of powdered 3 Å MS, trityl hexafluorophosphate (2.2 mmol), and the isoflavene **1b** (451 mg, 1.39 mmol) in freshly distilled, anhyd CH_2Cl_2 (50 mL, from CaH_2) was stirred at r.t. under nitrogen for 30 min. The commercially available 2-trimethylsilylthiazole (0.403g, 2.564 mmol) was then added and the reaction mixture was stirred for a further hour at r.t. The reaction mixture was then filtered, washed with CH_2Cl_2, concentrated under vacuum filtration, and subjected to silica gel chromatography, using CH_2Cl_2 as the mobile phase to afford the product as a creamy white solid (430 mg, 76%).

(14) **Data for Selected Compounds**

7-Acetoxy-3-*p*-acetoxyphenyl-2-cyano-2*H*-1-benzopyran (7b)

White solid; mp 156–158 °C. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, *J* = 8.7 Hz, 2 H, H-2′/6′), 7.23 (d, *J* = 8.0 Hz, 1 H, H-5), 7.18 (d, *J* = 8.6 Hz, 2 H, H-3′/5′), 6.97 (s, 1 H, H4), 6.85 (dd, *J* = 2.5, 8.1 Hz, 1 H, H-6), 6.84 (s, 1 H, H-8), 6.01 (s, 1 H, H-2), 2.32 (s, 3 H, CH_3), 2.30 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.1 (C=O), 168.9 (C=O), 151.9 (C7), 151.1 (C8a), 150.3 (C4′), 131.9 (C3), 128.3 (C5), 126.2 (C2′), 125.9 (C1′), 122.4 (C3′), 122.3 (C4), 119.1 (C4a), 117.0 (C6), 110.5 (C8), 64.3 (C2), 21.1 (CH_3). MS (CI$^+$): *m/z* (%) = 323 (100) [MH$^+$ – HCN]. Anal. Calcd (%) for $C_{20}H_{15}NO_5$: C, 68.76; H, 4.33; N, 4.01. Found: C, 69.20; H, 4.34; N, 3.67.

7-Acetoxy-3-*p*-acetoxyphenyl-2-(2-thiazoyl)-2*H*-1-benzopyran (8a)

Creamy white solid; mp 136–138 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.60 (br d, *J* = 2.7 Hz, 1 H, H-2″), 7.37 (d, *J* = 8.7 Hz, 2 H, H-2′/6′), 7.23 (d, *J* = 6.3 Hz, 1 H, H-5), 7.08 (d, *J* = 2.7 Hz, 1 H, H-3″), 6.93 (d, *J* = 8.4 Hz, 2 H, H-3′/5′), 6.89 (s, 1 H, H4), 6.57 (dd, *J* = 2.7, 8.4 Hz, 1 H, H-6), 6.53 (d, *J* = 2.4 Hz, 1 H,H-8), 6.44 (br s, 1 H, H-2), 2.13 (s, 3 H, CH_3), 2.10 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.5 (C=O), 169.3 (C=O), 169.3 (C1″), 151.8 (C7), 151.7 (C8a), 150.8 (C4′), 143.3 (C4″), 134.0 (C3), 131.5 (C1′), 127.9 (C5), 126.9 (C2′), 122.2 (C3′), 121.1 (C3″), 120.9 (C4), 120.2 (C4a), 115.7 (C6), 110.6 (C8), 74.7 (C2), 21.3 (CH_3). HRMS (CI$^+$): *m/z* calcd for [M + H]$^+$ $C_{22}H_{17}NO_5S$ + H: 408.0906; found: 408.0887.

7-Acetoxy-3-*p*-acetoxyphenyl-2-ethoxy-2*H*-1-benzopyran (8f)

Creamy white solid; mp 134–136 °C. ^{1}H NMR (300 MHz, $CDCl_3$): d = 7.53 (d, *J* = 9.0 Hz, 2 H, H-2′/6′), 7.23 (d, *J* = 8.4 Hz, 1 H, H-5), 7.12 (d, *J* = 8.4 Hz, 2 H, H-3′/5′), 6.98 (s, 1 H, H-4), 6.82 (d, *J* = 2.1 Hz, 1 H, H-8), 6.76 (dd, *J* = 8.4, 2.1 Hz, 1 H, H6), 5.95 (s, 1 H, H-2), 4.04–3.96 (m, 1 H, OCH_2CH$_3$), 3.82–3.74 (m, 1 H, OCH_2CH$_3$), 2.32 (s, 3 H, CH_3CO), 2.30 (s, 3 H, CH_3CO), 1.25 (t, *J* = 7.2 Hz, 3 H, CH$_2$CH_3). ^{13}C NMR (75 MHz, $CDCl_3$): d = 169.5 (C=O), 169.3 (C=O), 151.4 (C7), 151.1 (C8a), 150.6 (C4′), 134.6 (C3), 129.7 (C1′), 128.0 (C5), 126.9 (C2), 122.1 (C3′), 121.5 (C4), 119.6 (C4a), 115.4 (C6), 110.4 (C8), 97.2 (C2), 64.1 (*C*H$_2$CH$_3$), 21.5 (*C*H$_3$CO), 15.7 (CH$_2$*C*H$_3$). MS (CI$^+$): *m/z* (%) = 323 (100; 2-unsubstituted isoflavylium ion). Anal. Calcd (%) for $C_{21}H_{20}O_6$: C, 68.40; H, 5.48. Found: C, 68.49; H, 5.53.

7-Acetoxy-3-*p*-acetoxyphenyl-2-[2-(7-acetoxy-3-*p*-acetoxyphenyl-2*H*-1-benzopyranyl)ethynyl]-2*H*-1-benzopyran (9)

Solid; mp 237–238 °C (dec.). ^{1}H NMR (300 MHz, DMF-d_6; integrations and assignments for half dimer): d = 7.11 (d, *J* = 9.0 Hz, 2 H, H-2′/6′), 7.02 (d, *J* = 8.4 Hz, 1 H, H-5), 6.98 (s, 1 H, H4), 6.73 (dd, *J* = 2.4, 0.3 Hz, 1 H, H-8), 6.66 (d, *J* = 9.0 Hz, 1 H, H-3′), 6.53 (s, 1 H, H-2), 6.51 (dd, *J* = 8.4, 2.4 Hz, 1 H, H6), 1.94 (s, 3 H, CH_3), 1.88 (s, 3 H, CH_3). ^{13}C NMR (75 MHz, DMSO-d_6): d = 169.2 (C=O), 169.1 (C=O), 151.8 (C7), 150.8 (C8a), 150.2 (C4′), 133.0 (C3), 128.4 (C1′), 128.2 (C5), 126.4 (C2′), 122.2 (C4), 121.5 (C3′), 119.4 (C6), 116.3 (C4a), 110.7 (C8), 92.5 (ethynyl C), 91.7 (C2), 20.4 (CH_3), 20.3 (CH_3). MS (ES$^+$): *m/z* (%) = 323 (100; 2-unsubstituted isoflavylium ion). Anal. Calcd (%) for $C_{41}H_{34}O_{10}$: C, 69.28; H, 4.60. Found: C, 69.27; H, 4.62.