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Highly Selective One-Pot Synthesis of Polysubstituted Isoflavanes using Styryl Ethers and Electron-Withdrawing *ortho*-Quinone Methides Generated In Situ

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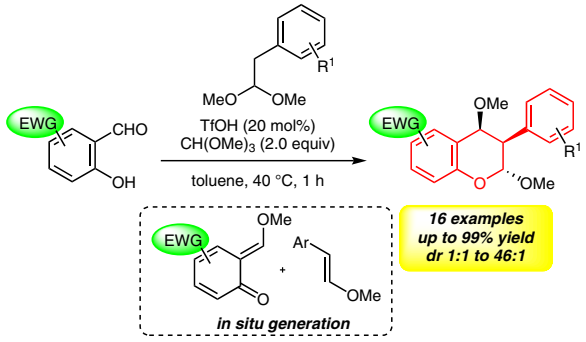

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Abstract A highly selective one-pot synthesis of polysubstituted isoflavanes has been developed. The reaction proceeds through the cycloaddition of methyl styryl ethers, derived from phenylacetaldehyde dimethyl acetals under acidic conditions, with electron-withdrawing *ortho*-quinone methides generated in situ. When phenylacetaldehyde dimethyl acetals were reacted with salicylaldehydes, the reaction proceeded smoothly to afford the corresponding isoflavanes stereoselectively in high yields and with excellent regioselectivities. The present reaction provides versatile access to functionalized isoflavanes, and constitutes a useful tool for the synthesis of biologically active molecules.

Key words isoflavan, *ortho*-quinone methide, [4+2] cycloaddition, stereoselective synthesis, regioselective synthesis

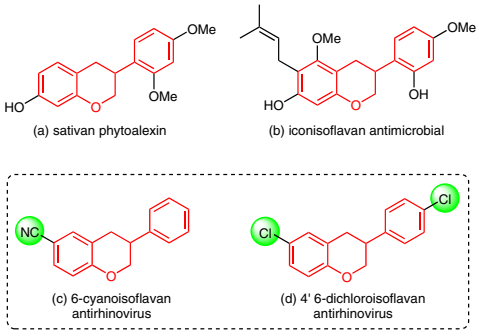
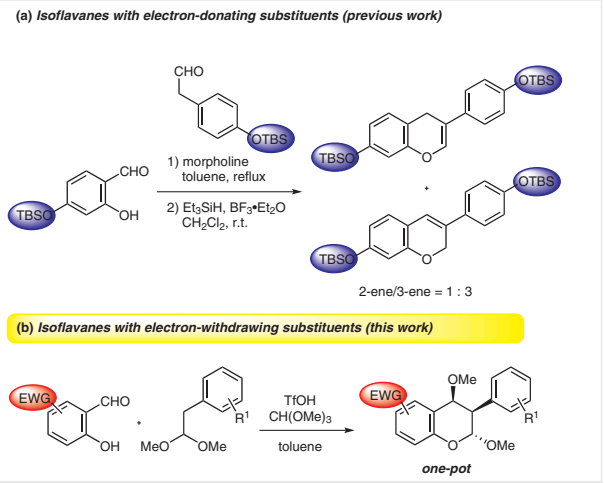


Figure 1 Selected examples of bioactive compounds of isoflavanes

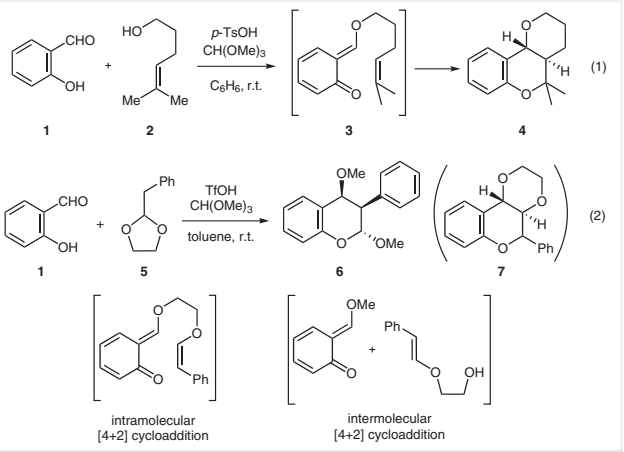
Isoflavan is a prevalent structural motif found in numerous natural products and pharmaceuticals, which display diverse biological activities such as antioxidant and antimicrobial action.[1] Many biologically active isoflavanes bear multiple substituents, and, in particular, have various electron-donating groups such as methoxy groups (Figure 1a and 1b). Based on the structure of these compounds, a number of research groups have developed methodologies to synthesize isoflavanes possessing electron-donating groups (Scheme 1a).[2] In contrast, isoflavanes substituted with electron-withdrawing groups have received little attention in organic synthetic chemistry. Some isoflavanes having electron-withdrawing substituents are known to exhibit biological activity such as anti-rhinovirus action (Figure 1c and 1d).[3] Despite the reports of these functionalities of isoflavanes, the synthesis of such electron-withdrawing compounds has been much less explored. In addition, a few previous synthetic reports suffered from the requirement of tedious reaction process;[3] therefore, more convenient synthetic methodology remains desirable.

ortho-Quinone methide (*o*-QM) is a useful synthetic intermediate that is widely implicated in organic synthesis.[4] In recent years, catalytic asymmetric reactions using *o*-QM are rapidly growing areas and have been examined by several research groups.[5] Recently, we have been developing the generation of *o*-QM from salicylaldehyde in the presence of acid catalyst and trimethyl orthoformate under mild conditions.[6] In the course of this study, we reported that salicylaldehyde **1** reacted with unsaturated alcohol **2** in benzene in the presence of *p*-TsOH and trimethyl orthoformate to give *trans*-**4** through intramolecular inverse-electron-demand [4+2] cycloaddition reaction of **3** (Scheme 2, Equation (1)).[7] In this context, when we attempted to use acetal **5** instead of alcohol **2**, which would be converted into the unsaturated alcohol under acidic conditions, interestingly, isoflavan **6** was obtained in 52% yield, and no flavan **7** was observed (Scheme 2, Equation (2)). It is considered that the reaction would proceed through intermolecular [4+2] cycloaddition of *ortho*-quinone methide with unsaturated

alcohol. The reaction prompted us to investigate a new method giving a one-pot synthesis of isoflavanes bearing electron-withdrawing groups. Herein, we report the highly selective one-pot synthesis of polysubstituted isoflavanes using styryl ethers and electron-withdrawing *ortho*-quinone methides generated in situ (Scheme 1b).



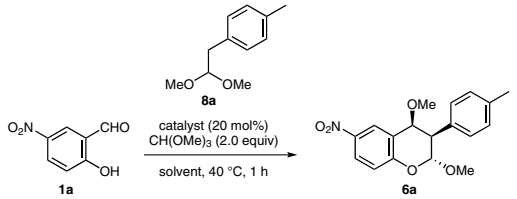
Scheme 1 The synthesis of isoflavanes



Scheme 2 The reactions of salicylaldehyde **1** with alcohol **2** or acetal **5**

We initially investigated the reaction of 5-nitrosalicylaldehyde (**1a**) with 2-(4-methylphenyl)acetaldehyde dimethyl acetal (**8a**) using Lewis and Brønsted acid catalysts in various solvents at 40 °C. While a soft Lewis acid catalyst gave no product (Table 1, entry 1), the use of $Sc(OTf)_3$, a hard Lewis acid catalyst, afforded the desired cycloadduct **6a** (entry 3). Although *p*-TsOH·H_2O and HBF_4·OEt_2 gave low yields (entries 4 and 5), a stronger Brønsted acid, TfOH, smoothly led to the formation of the corresponding product in high yield (dr 30:1, entry 6).[8] The reaction in a medium polar solvent such as 1,2-dichloroethane (DCE) and tetrahydrofuran (THF), afforded good yields (entries 7 and 8). A high polar solvent, CH_3CN, was also suitable for the reaction (entry 9). Decreasing the amount of catalyst did not improve the yield (entry 10). Interestingly, the reaction without trimethyl orthoformate also gave the desired product in 63% yield (entry 11). Clearly, an acetal exchange reaction between salicylaldehyde **1a** and acetal **8a** proceeded to generate *o*-QM and vinyl ether, while trimethyl orthoformate effectively generated *o*-QM from salicylaldehyde. The best yield of the desired product was achieved with **1a** (0.25 mmol), **8a** (0.75 mmol), $CH(OMe)_3$ (2.0 equiv), TfOH (20 mol%) in toluene at 40 °C (entry 6).

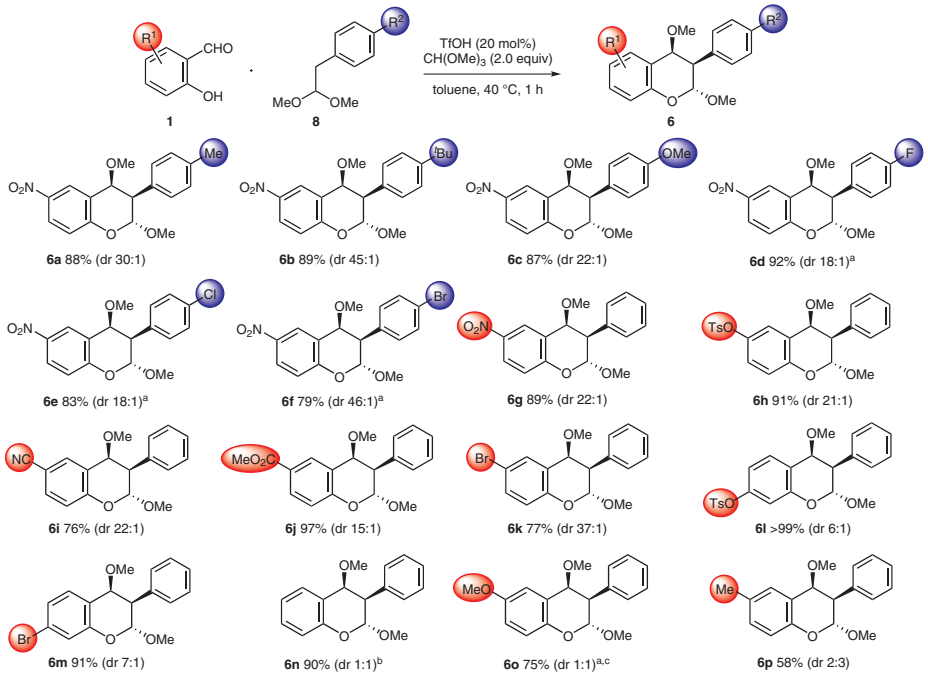
Table 1 Optimization of the Reaction Conditions[a]



Entry	Solvent	Catalyst	Yield (%)
1	toluene	$Pd(OAc)_2$	N.R.
2	toluene	BF_3·OE_2	N.R.
3[b]	toluene	$Sc(OTf)_3$	12
4[b]	toluene	*p*-TsOH·H_2O	12
5[b]	toluene	HBF_4·OEt_2	9
6	toluene	TfOH	84
7	DCE	TfOH	82
8	THF	TfOH	73
9	CH_3CN	TfOH	74
10[c]	toluene	TfOH	73
11[d]	toluene	TfOH	63

[a] All reactions were carried out with **1a** (0.25 mmol), **8a** (0.75 mmol), $CH(OMe)_3$ (2.0 equiv), catalyst (20 mol%) in solvent (2.5 mL) at 40 °C for 1 h.
[b] Yield based on ^1H NMR spectra.
[c] The amount of TfOH was 10 mol%
[d] Without $CH(OMe)_3$

With the optimal reaction conditions in hand, the generality of various salicylaldehydes and phenylacetaldehyde dimethyl acetal was examined (Scheme 3). The phenylacetaldehyde dimethyl acetals possessing electron-donating groups such as methyl, *tert*-butyl and methoxy groups afforded the target products **6a–c** in good yields and diastereoselectivities. The substrates having halogen groups were also suitable in the reaction (**6d–f**). The reaction of the parent substrate phenylacetaldehyde dimethyl acetal proceeded efficiently to give **6g**. Fortunately, a good crystal for X-ray analysis was obtained in this case. The relative stereochemistry of the major diastereomer of isoflavan **6g** was determined by X-ray crystal structure analysis to be



Scheme 3 The reaction of salicylaldehydes **1** with phenylacetaldehyde dimethylacetal **8**. The diastereomeric ratio was based on ^{1}H NMR spectroscopic analysis. [a] 24 h, [b] 2 h, [c] room temperature

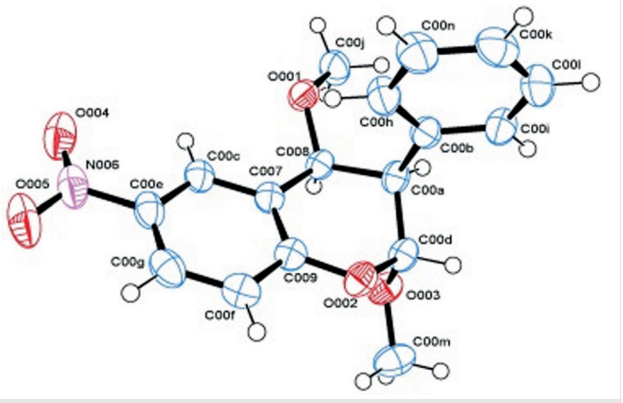
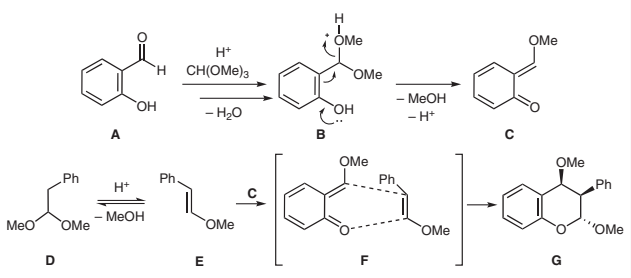


Figure 2 ORTEP view of isoflavan **6g**[9]

(2*RS*,3*RS*,4*SR*), as shown in Figure 2.[9] When salicylaldehydes bearing the strong or medium electron-withdrawing groups such as 5-tosyloxy, 5-nitrile, 5-methoxycarbonyl and 5-bromo were used, the corresponding products **6h–k** were obtained in good yields. It is reported that 6-cyanoisoflavan exhibits antirhinovirus activity.[3a] While 4-tosyloxy, 4-bromo and parent salicylaldehydes gave high yields (**6l** and **6m**), diastereoselectivities were clearly decreased compared with 5-substituted salicylaldehydes. When salicylaldehyde having electron-donating groups were used, moderate yields and low diastereoselectivities were observed (**6o** and **6p**). According to the previous studies,[10] 4-hydroxy- or 4-methoxy-chromanes possessing electron-donating groups usually suffer racemization at the 4-position under acidic conditions. Therefore, **6o** and **6p** should be obtained with lower diastereoselectivities through racemization at 4-position. The reaction was well suitable for the use of electron-withdrawing salicylaldehydes and various phenylacetaldehyde dimethyl acetals.

A proposed mechanism for the present reaction is shown in Scheme 4. *o*-QM **C** is generated from salicylaldehyde **A** and trimethyl orthoformate via acetal **B** under acidic conditions. Elimination of methanol from dimethyl acetal **D** generates methyl styryl ether **E**. According to previous studies, [4+2] cycloaddition of vinyl ethers would be through a concerted reaction mechanism.[11] Based on the above, the electron-rich vinyl ether **E** would react with *o*-QM **C** through a concerted reaction to give the desired cyclic product **G** with excellent regioselectivity.[2b,2c] As shown in Scheme 2, high diastereoselectivities were observed when salicylaldehydes having 5-substituted electron-withdrawing groups were used, and it is considered that the observed stereochemistry would be achieved via an *endo* transition-state intermediate.[11]

In conclusion, we have developed a highly selective one-pot synthesis of polysubstituted isoflavanes using styryl ethers and electron-withdrawing *ortho*-quinone methides generated in situ. When phenylacetaldehyde dimethyl acetals were reacted with salicylaldehydes, the highly regioselective reaction proceeded to afford the corresponding isoflavanes in high yields. In particular, a variety of salicyl-



Scheme 4 The proposed reaction mechanism

aldehydes having electron-withdrawing groups with phenylacetaldehyde dimethyl acetals gave good regio- and diastereoselectivities. The present reaction provides versatile access to functionalized isoflavanes, and constitutes a useful tool for the synthesis of biologically active molecules.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611361.

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(8) **Synthesis of Isoflavane 6; General Procedure**: Salicylaldehyde **1** (0.25 mmol), phenylacetaldehyde dimethyl acetal **8** (0.75 mmol) and trimethyl orthoformate (0.50 mmol) were dissolved in anhydrous toluene (2.5 mL) under nitrogen. Trifluoromethanesulfonic acid (20 mol%) was added into the reaction mixture. After being stirred at 40 °C for 1 h, the reaction was quenched with 5% aq. $NaHCO_3$. The organic layer was separated and the aqueous layer was extracted with ethyl acetate. The combined organic layer was dried over $MgSO_4$, and filtered. The filtrate was concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane/ethyl acetate, 50:1) to afford isoflavan **6**. Characterization data for 2,4-dimethoxy-6-nitro-3-(*p*-tolyl)phenylchromane (**6a**): Yield: 0.1368 g (84%); yellow solid; dr 30:1. ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.29 (dd, *J* = 2.7, 0.8 Hz, 1 H), 8.16 (dd, *J* = 8.7, 3.0 Hz, 1 H), 7.10 (d, *J* = 1.3 Hz, 4 H), 7.00 (d, *J* = 1.3 Hz, 1 H), 5.50–5.47 (m, 1 H), 4.59 (d, *J* = 4.7 Hz, 1 H), 3.55 (s, 3 H), 3.48 (t, *J* = 5.0 Hz, 1 H), 3.38 (s, 3 H), 2.31 (s, 3 H); ^{13}C NMR (126 MHz, $CDCl_3$): δ = 157.5, 141.6, 137.1, 132.6, 129.1, 128.9, 125.4, 124.4, 123.8, 117.3, 103.3, 74.4, 57.1, 56.6, 45.1, 21.0; IR (ATR): 2916, 1516, 1338, 1107, 1061, 1030, 918, 753, 616 cm^{-1}; HRMS (ESI+): *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{20}NO_5$: 330.1336; found: 330.1342.

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