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Article

Optimization of the Reaction Conditions for the Synthesis of Dihydrobenzofuran Neolignans

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We have optimized the experimental conditions for the silver(I)-promoted oxidative coupling of methyl *p*-coumarate (**I**) and methyl ferulate (**II**), which is the most frequently used methodology to synthesize the bioactive dihydrobenzofuran neolignans **1** ((±)-*trans*-dehydrodicoumarate dimethyl ester) and **2** ((±)-*trans*-dehydrodiferulate dimethyl ester). Most of the tested conditions affected the conversion (i.e., the consumption of **I** and **II**) and the selectivity (i.e., the percentage of **I** and **II** that was converted into **1** and **2**, respectively), so the optimized conditions were the ones that afforded the best balance between conversion and selectivity. Silver(I) oxide (0.5 equiv.) is the most efficient oxidant agent amongst the silver(I) reagents that were tested to convert methyl esters **I** and **II** into compounds **1** and **2**, respectively. Acetonitrile, which has not yet been reported as a solvent for this reaction, provided the best balance between conversion and selectivity, besides being "greener" than other solvents that are more often employed (e.g., dichloromethane and benzene). Under the optimized conditions, the reaction time decreased from 20 to 4 h without significantly impacting the conversion and selectivity.

Keywords: benzofuran derivatives, oxidative coupling, phenylpropanoids, radical intermediates

Introduction

Dihydrobenzofuran neolignans (DBNs) are compounds that are biosynthesized by plants as part of their secondary metabolism. DBNs result from oxidative coupling of two propenylphenols (C_6C_3), which are joined through C8–C5' and C7–O4' bonds.[1,2] Natural and synthetic DBNs exhibit diverse biological activities, such as anti-inflammatory,[3] antioxidant,[3] cytotoxic,[4] schistosomicidal,[5] leishmanicidal,[6] and insecticidal actions,[7] among others.

Despite the various synthetic methodologies that have been reported in the literature for the synthesis of DBNs (e.g., intramolecular C–H insertion[8] and sequential cross-metathesis/isomerization/allylboration),[9] oxidative coupling of phenylpropanoids, which mimics DBN biosynthesis in plants and affords the dihydrobenzofuran skeleton in only one synthetic step under mild conditions, is still the most commonly used.[2] Silver(I) oxide is the classic oxidant that is employed to promote this coupling. In the mechanism proposed in the literature[10] for the silver(I)-promoted oxidative coupling of phenylpropanoids, the first step consists of 4–OH bond homolysis, to generate the phenoxy radical intermediate **B** (Scheme 1). In preliminary studies, mass spectrometry has been used to track changes in the reaction mixture with time. These studies suggested that the phenoxy radical originates from oxidation of a phenolate anion **A** and consequent silver(I) reduction to silver(0), which precipitates in the reaction vessel internal walls (data not published) (Scheme 1). Next, a C5'–C8 bond is supposedly established between two phenoxy radical units, which is followed by ring closure (resulting from O4–C7' bond formation) and further tautomerization.

The silver(I) oxide-promoted oxidative coupling of phenylpropanoids is diastereoselective and gives DBNs as racemic mixtures of *trans*-enantiomers in 20-40% yield.[10,11] Many efforts have been dedicated to replacing silver(I) oxide in this reaction to obtain DBN in higher stereoselectivity and yields. To this end, iron salts,[12] Ru and Rh complexes,[13] the horseradish peroxidase (HRP)/H_2O_2 system,[14] and laccases have been employed.[15] However, stereoselectivity obtained for other metals than silver(I) in the oxidative coupling of phenylpropanoids to give DBNs

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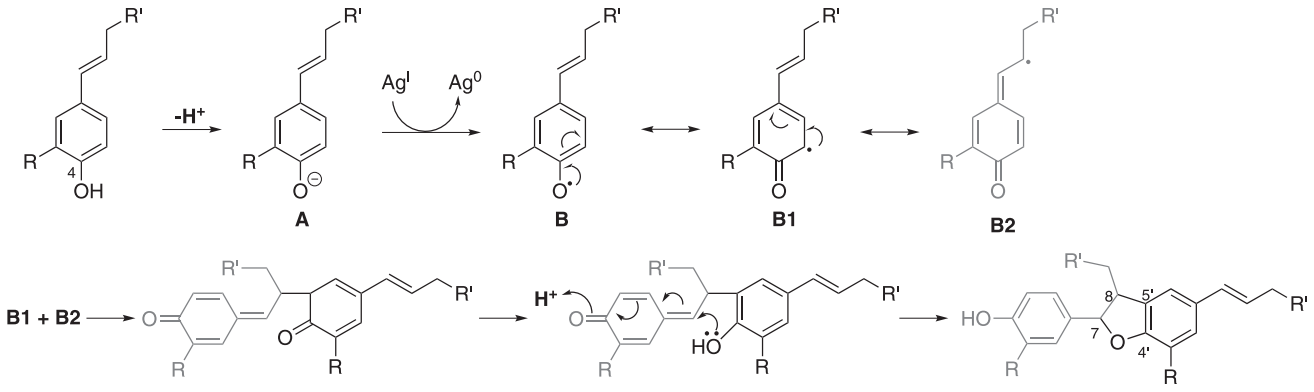


Scheme 1. Mechanism proposed for the silver(I) oxide-promoted oxidative coupling of phenylpropanoids to give dihydrobenzofuran neolignans (adapted from Daquino *et al.*).[10]

has not been clearly described.[12,13] On the other hand, some of these methods have provided good enantioselectivity (e.g., HRP/H_2O_2 system and laccases) and increased yields. Nevertheless, the high cost or the experimental complexity[8,9] as compared to the use of silver(I) oxide still makes the methodology based on silver(I) oxide more attractive.

In this paper, we have systematically investigated reaction conditions to optimize the silver(I)-promoted oxidative coupling of phenylpropanoids.

Experimental

General

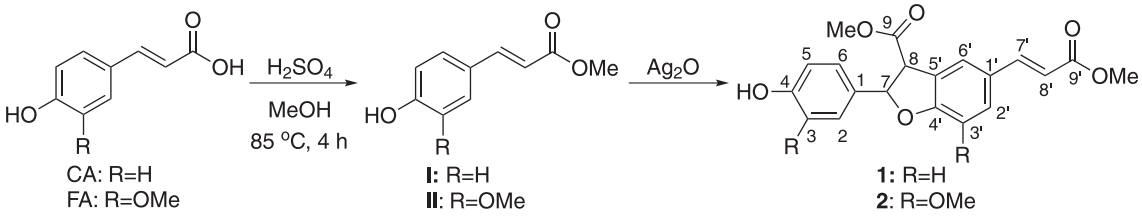
The ^{1}H and ^{13}C nuclear magnetic resonance (NMR) analyses were performed on a Bruker Advance DRX400 spectrometer (Karlsruhe, Germany; 400.13 MHz for ^{1}H and 100.61 MHz for ^{13}C), as described in the literature.[11] The samples were dissolved in acetone-d_6 (99.8 atom% D, Sigma-Aldrich, St. Louis, USA); tetramethylsilane (TMS, 0.01%) was used as internal standard. The chemical shifts (δ) were expressed in parts *per* million (ppm) in relation to the residual solvent peak, and the multiplicity of signals was deduced according to the signals obtained in spectrum. The coupling constants (J, in Hz) were calculated in comparison to the same signal peaks, and the relative integral was deduced according to the number of hydrogens.

The infrared (IR) spectra were recorded on a spectrophotometer IR Spectrum Two (PerkinElmer, Beaconsfield, UK). The samples were macerated in potassium bromide (99.99%, Sigma-Aldrich, St. Louis, USA) and fused in a pellet under pressure.

The mass spectra were recorded on a gas chromatograph-mass spectrometer (GC-MS) Shimadzu QP2010-Plus (Kyoto, Japan) system equipped with an AOC-20i autosampler and an RTX-5MS (Restek Co., Bellefonte, PA, USA) fused silica capillary (30 m × 0.25 mm inner diameter, 0.25-μm film thickness). The electron ionization mode was used at 70 eV. Helium (99.999%) was employed as the carrier gas at a constant flow of 1.0 mL min^{-1}. The injection volume was 0.1 μL (split ratio of 1:10). The injector and the ion-source temperatures were set at 280 and 300 °C, respectively. The oven temperature was programmed to rise from 110 to 300 °C at 10 °C min^{-1} and then held at 300 °C for 5 min. The mass spectra were taken with a scan interval of 0.5 s for masses ranging from 40 to 600 Da.

Synthesis of the dihydrobenzofuran neolignans **1** and **2**

The dihydrobenzofuran neolignans (DBNs) **1** and **2**, which were used as standards, were synthesized by oxidative coupling of methyl *p*-coumarate (**I**) and methyl ferulate (**II**), respectively, in the presence of silver(I) oxide, as oxidant, as reported previously (Scheme 2).[4,7,11,16]



Scheme 2. Synthesis of the dihydrobenzofuran neolignans **1** and **2** by silver(I)-oxide oxidative coupling of methyl *p*-coumarate (**I**) and methyl ferulate (**II**), respectively (adapted from references 4,7,11,16).

Methyl *p*-coumarate (**I**) was obtained from coumaric acid (CA, 3.0 g, 18.3 mmol) (Sigma-Aldrich, St. Louis, USA), which was dissolved in 30 mL of methanol in a 100-mL round-bottom flask, followed by addition of 1 mL of sulfuric acid. Methyl ferulate (**II**) was synthesized from ferulic acid (FA, 3.0 g, 15.4 mmol) (Sigma-Aldrich, St. Louis, USA), which was dissolved in 180 mL of methanol in a 500-mL round-bottom flask, followed by addition of 3 mL of sulfuric acid. The reaction mixtures were kept under reflux at 85 °C for 4 h. After methanol was removed under reduced pressure, the resulting crude products were dissolved in ethyl acetate and extracted with water and a saturated $NaHCO_3$ solution (3 × 30 mL). The organic phase was dried over $MgSO_4$ and filtered. Ethyl acetate was removed from the samples under reduced pressure to afford compounds **I** and **II** as a yellowish powder and a brown powder in 94 and 95% yield, respectively.

Next, 3.0 g of methyl ester **I** (16.8 mmol) or **II** (14.4 mmol) were added to a two-neck 100-mL round-bottom flask covered with aluminum foil and dissolved in 40 mL of a benzene/acetone (6:4) mixture under magnetic stirring and nitrogen atmosphere. Next, silver(I) oxide (8.5 mmol) (Sigma-Aldrich, St. Louis, USA) was added, and the reaction progress was monitored by thin layer chromatography (TLC) for 4 h. The reaction mixture was filtered off, and the solvent was removed under reduced pressure. The crude products were purified by column chromatography as previously reported,[11] to afford compounds **1** (35% yield) and **2** (42% yield) as mixtures of *trans*-enantiomers.

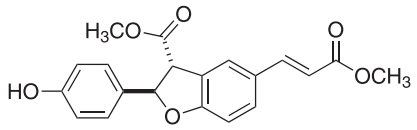
Methyl *p*-coumarate (**I**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* 16.1 Hz, 1H, H-1'), 7.45 (d, *J* 8.6 Hz, 2H, H-2 and H-6), 6.85 (d, *J* 8.6 Hz, 2H, H-3 and H-5), 6.31 (d, *J* 16.1 Hz, 1H, H-2'), 5.03 (br s, 1H, OH), 3.80 (s, 3H, H-4'); EI-MS (70 eV, *m/z*, relative intensity / %): 178 [$M^{\bullet+}$] (100), 147 [$M^{\bullet+}$ – •OCH_3] (90), 119 [$M^{\bullet+}$ – •OCH_3 – CO] (90), 91 [$M^{\bullet+}$ – •OCH_3 – CO – CO] (25). The NMR data are in agreement with the literature.[17]

Methyl ferulate (**II**)

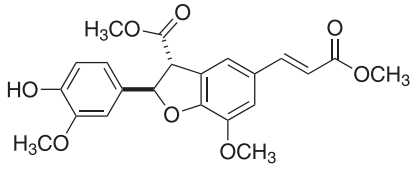
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* 16.0 Hz, 1H, H-1'), 7.08 (dd, *J* 1.9, 8.1 Hz, 1H, H-2), 7.04 (d, *J* 1.9 Hz, 1H, H-6), 6.93 (d, *J* 8.1 Hz, 1H, H-3), 6.30 (d, *J* 16.0 Hz, 1H, H-2'), 5.89 (br s, 1H, OH), 3.93 (s, 3H, H-7), 3.80 (s, 3H, H-4'); EI-MS (70 eV, *m/z*, relative intensity / %): 208 [$M^{\bullet+}$] (100), 177 [$M^{\bullet+}$ – •OCH_3] (60), 145 [$M^{\bullet+}$ – •OCH_3 – CH_3OH] (40), 117 [$M^{\bullet+}$ – •OCH_3 – CH_3OH – CO] (22). The NMR data are in agreement with the literature.[17]

(±)-*trans*-Dehydrodicoumarate dimethyl ester (**1**)



Yellow powder; mp 105-107 °C; IR (KBr pellet) ν_{max} / cm^{-1} 3384 (–OH), 2955 (C_{sp2}–H), 1715 (C=O), 1602 (C=C), 1490 (C=C), 1440 (C=C), 1240 (C–O), 1115 (C–O); ^{1}H NMR (400 MHz, acetone-d_6) δ 7.65 (1H, d, *J* 16.0, H7'), 7.62 (1H, br s, H6'), 7.50 (1H, dd, *J* 1.5 and 8.1 Hz, H2'), 7.28 (2H, dd, *J* 1.8 and 6.8 Hz, H2 and H6), 6.91 (1H, d, *J* 8.1 Hz, H3'), 6.87 (2H, dd, *J* 1.8 and 6.8 Hz, H5), 6.41 (1H, d, *J* 16.0 Hz, H8'), 6.03 (1H, d, *J* 7.3 Hz, H7), 4.40 (1H, d, *J* 7.3 Hz, H8), 3.81 (3H, s, H10), 3.73 (3H, s, H10'); ^{13}C NMR (100 MHz, acetone-d_6) δ 172.0 (C, C9), 168.2 (C, C9'), 162.6 (C, C4), 159.1 (C, C4'), 145.5 (CH, C7'), 132.1 (C, C1'), 131.3 (C, C1), 128.9 (CH, C2 and C6), 128.0 (CH, C2'), 126.9 (C), 126.5 (CH, C6'), 116.9 (CH, C3 and C5), 116.5 (CH, C8'), 111.2 (CH, C3'), 88.2 (CH, C7), 56.0 (CH, C8), 53.4 (CH_3, C10'), 52.0 (CH_3, C10); EI-MS (70 eV, *m/z*, relative intensity / %): 354 [$M^{\bullet+}$] (26), 322 [$M^{\bullet+}$ – CH_3OH] (30), 290 [$M^{\bullet+}$ – CH_3OH – CH_3OH] (100). The NMR data are in agreement with the literature.[11]

(±)-*trans*-Dehydrodiferulate dimethyl ester (**2**)



Yellow oil; IR (KBr pellet) ν_{max} / cm^{-1} 3395 (–OH), 2951 ($C_{sp}{}^2$–H), 1740 (C=O), 1723 (C=O), 1644 (C=C), 1594 (C=C), 1523 (C=C), 1432 (C=C), 1269 (C–O), 1165 (C–O), 1140 (C–O), 1095 (C–O), 1036 (C–O), 982, 941, 853; ^{1}H NMR (400 MHz, acetone-d_6) δ 7.63 (1H, d, *J* 16.1 Hz, H7'), 7.33 (1H, br s, H2'), 7.29 (1H, br s, H6'), 7.10 (1H, d, *J* 1.7 Hz, H2), 6.92 (1H, dd, *J* 8.1, 1.7 Hz, H6), 6.84 (1H, d, *J* 8.1 Hz, H5), 6.44 (1H, d, *J* 16.1 Hz, H8'), 6.04 (1H, d, *J* 7.3 Hz, H7), 4.47 (1H, d, *J* 7.3 Hz, H8), 3.92 (3H, s, H11'), 3.84 (3H, s, H11'), 3.81 (3H, s, H10'), 3.73 (3H, s, H10'); ^{13}C NMR (100 MHz, acetone-d_6) δ 172.1 (C, C9), 168.2 (C, C9'), 151.5 (C, C4'), 149.0 (C, C3), 148.5 (C, C4), 146.3 (C, C3'), 145.9 (CH, C7'), 132.5 (C, C1), 129.9 (C, C1'), 127.8 (C, C5'), 120.7 (CH, C6), 119.4 (CH, C6'), 116.7 (CH, C8'), 116.3 (CH, C5), 113.9 (CH, C2'), 111.2 (CH, C2), 88.8 (CH, C7), 56.9 (CH_3, C11'), 56.8 (CH_3, C11'), 56.4 (CH, C8), 53.5 (CH_3, C10'), 52.0 (CH_3, C10'); EI-MS (70 eV, *m/z*, relative intensity / %): 414 [$M^{\bullet+}$] (5), 382 [$M^{\bullet+}$ – CH_3OH] (90), 350 [$M^{\bullet+}$ – CH_3OH – CH_3OH] (70). The NMR data are in agreement with the literature.[11]

GC analyses

The consumption of methyl esters **I** and **II** (i.e., conversion) and the formation of the DBNs **1** and **2** (i.e., selectivity) were monitored on a gas chromatograph GC-2010 Plus Shimadzu (Kyoto, Japan) fitted with a flame ionization detector (FID) detector and an RTX-5 fused silica capillary column (30 m × 0.25 mm i.d., 0.25-μm film thickness). For this purpose, 20-μL aliquots were sampled from the reaction mixture at pre-determined times (1, 2, 3, 4, and 20 h) and transferred to a 1-mL Eppendorf plastic vial. The samples were filtered off to remove the oxidant; added to a 1-mL vial containing 200 μL of ethyl acetate for dilution; and injected into the gas chromatograph. The temperature was programmed to increase from 70 to 310 °C at 15 °C min^{-1} in 30 min. The substances of interest were identified by comparison with retention times of standard samples.

Results and Discussion

Optimization of the nature and concentration of the oxidant

Although silver(I) oxide is the most commonly employed oxidant in the synthesis of dihydrobenzofuran neolignans via oxidative coupling of phenylpropanoids, different stoichiometries and reaction conditions have been reported. For instance, Lemière *et al.*[18] used 1 equiv. of substrate **II** and 0.5 equiv. of the oxidant (Ag_2O) in a dry benzene/acetone (5:3 v/v) mixture at room temperature for 20 h, which afforded DBN **2** in 31% yield ([substrate] = 0.18 mol L^{-1}; [oxidant] = 0.09 mol L^{-1}). Pieters *et al.*[17] used 1 equiv. of substrate **I** and 0.7 equiv. of Ag_2O in a dry benzene/acetone (7:5 v/v) mixture ([substrate] = 0.23 mol L^{-1}; [oxidant] = 0.16 mol L^{-1}) at room temperature for 65 h, to obtain DBN **1** in 23% yield. In turn, Orlandi *et al.*[19] employed 1 equiv. of substrate **II** and 1.6 equiv. of Ag_2O under inert atmosphere (Ar or N_2) in dry CH_2Cl_2 ([substrate] = 0.10 mol L^{-1}; [oxidant] = 0.16 mol L^{-1}) for 20-24 h at room temperature, which gave DBN **2** in 32% yield. Daquino *et al.*[10] used 1 equiv. of methyl caffeate (substrate) and 1 equiv. of Ag_2O in $CHCl_3$ at room temperature for 2 h, to obtain the corresponding DBN in 17.6% yield ([substrate] = [oxidant] = 0.07 mol L^{-1}). Therefore, to date, there are no standard conditions regarding the use of silver(I) oxide as oxidant in the oxidative coupling of phenylpropanoids.

We started optimizing the oxidative coupling reaction conditions by investigating the oxidant. Sako *et al.*[20] evaluated how different silver(I) reagents (e.g., AgOAc, Ag_2O, Ag_2CO_3, and $AgNO_3$) affected the synthesis of the resveratrol dehydrodimer and obtained yields between 4 and 97%. Thus, we decided to examine how the use of silver(I) reagents other than Ag_2O impacted the oxidative coupling of methyl esters **I** and **II**. First, we employed 1 equiv. of methyl ester **I** or **II** (0.56 mmol) and 1 equiv. of Ag^+ ions (0.56 mmol) dissolved in 2 mL of benzene/acetone (6:4 v/v) under magnetic stirring. Besides Ag_2O and $AgNO_3$ (Merck, Darmstadt, Germany), which have already been reported[20] as oxidants in this reaction, we also tested AgBr (Merck, Darmstadt, Germany), $AgOCOCF_3$ (Aldrich, St. Louis, USA), and $AgOSO_2CF_3$ (Merck, Darmstadt, Germany). The conversion (C) and the selectivity (S) obtained from GC-FID analyses are shown in Tables 1 (methyl ester **I** → DBN **1**) and 2 (methyl ester **II** → DBN **2**).

Under the same experimental conditions, methyl ferulate (**II**) conversion (i.e., the percentage of methyl ester that was consumed) was higher than methyl *p*-coumarate (**I**) conversion, regardless of the oxidant. On the other hand, selectivity (i.e., the percentage of methyl ester that was converted into the corresponding DBN) was higher for methyl *p*-coumarate (**I**) as compared to methyl ferulate (**II**). This difference in the conversion of methyl esters **I** and **II** and in the selectivity toward DBNs **1** and **2**, respectively, could explain, at least in principle, the lack of standard

Table 1. Methyl ester **I** (methyl *p*-coumarate) conversion (C) and selectivity (S) toward dihydrobenzofuran neolignan (DBN) **1** as a function of the silver(I) reagent, used as oxidant

0.56 mmol 1 equiv. Ag^+	Ag_2O 0.14 mol L^{-1}		$AgNO_3$ 0.28 mol L^{-1}		AgBr 0.28 mol L^{-1}		$AgOCOCF_3$ 0.28 mol L^{-1}		$AgOSO_2CF_3$ 0.28 mol L^{-1}	
Reaction time / h	C / %	S / %	C / %	S / %	C / %	S / %	C / %	S / %	C / %	S / %
1	9.8	61.7	1.0	5.0	0.8	3.8	11.8	88.3	2.1	6.5
2	17.2	94.0	0.3	20.0	0.4	12.6	16.8	91.6	9.5	1.2
3	24.8	82.0	0.4	14.0	0.2	55.0	20.3	83.3	13.2	11.8
4	32.7	94.0	0.5	32.0	0.3	6.7	20.5	91.1	37.4	0.0
20	35.3	66.4	1.4	22.9	1.5	7.1	20.0	78.2	5.7	2.8

Table 2. Methyl ester **II** (methyl ferulate) conversion (C) and selectivity (S) toward dihydrobenzofuran neolignan (DBN) **2** as a function of the silver(I) reagent, used as oxidant

0.56 mmol 1 equiv. Ag^+	Ag_2O 0.14 mol L^{-1}		$AgNO_3$ 0.28 mol L^{-1}		AgBr 0.28 mol L^{-1}		$AgOCOCF_3$ 0.28 mol L^{-1}		$AgOSO_2CF_3$ 0.28 mol L^{-1}	
Reaction time / h	C / %	S / %	C / %	S / %	C / %	S / %	C / %	S / %	C / %	S / %
1	29.6	62.5	5.0	0.0	4.6	1.9	20.2	49.8	59.2	1.4
2	52.9	85.0	4.0	5.8	4.4	3.7	25.8	61.9	75.1	1.4
3	63.7	83.1	4.2	11.0	4.1	3.7	25.1	63.9	95.7	1.6
4	67.7	85.8	4.3	10.8	4.4	2.3	26.3	62.8	99.9	0.0
20	52.7	62.1	10.7	2.4	5.2	1.9	16.7	50.6	27.7	1.6

conditions for the silver(I) oxide-promoted oxidative coupling reaction. However, we found that Ag_2O was the most efficient oxidant because it provided the best balance between conversion and selectivity, especially for a reaction time of 4 h: 32.7% conversion of methyl ester **I** and 94.0% selectivity toward DBN **1**; 67.7% conversion of methyl ester **II** and 85.8% selectivity toward DBN **2**. It is noteworthy that the use of $AgCO_2CF_3$ afforded good conversion and selectivity percentages even though these values were not as high as for Ag_2O.

In the literature,[2,19] Ag_2O between 0.5 and 1.6 equiv. has been employed in the oxidative coupling of phenylpropanoids (oxidant concentrations ranging between 0.07 and 0.16 mol L^{-1}). Here, we evaluated how different Ag_2O concentrations affected the oxidative coupling of methyl esters **I** and **II** to produce DBNs **1** and **2**, respectively. To this end, we dissolved the methyl ester (1 equiv., 0.56 mmol) in a benzene/acetone (6:4 v/v, 2 mL) mixture and added the resulting solution to a round-bottom flask containing the oxidant and kept the reaction mixture under N_2 atmosphere for 20 h, covered with an aluminum foil. The oxidant impacted both the conversion and selectivity, as depicted in Tables 3 and 4. Larger Ag_2O amounts increased methyl ester conversion. On the other hand, larger Ag_2O amounts also decreased selectivity, which indicated that side reactions probably occurred when larger Ag_2O amounts were used. The best balance between conversion and selectivity was obtained for 0.5 equiv. of Ag_2O.

Table 3. Methyl ester **I** (methyl *p*-coumarate) conversion (C) and selectivity (S) toward dihydrobenzofuran neolignan (DBN) **1** as a function of the Ag_2O amount

Reaction time / h	0.25 equiv. 0.035 mol L^{-1}		0.5 equiv. 0.07 mol L^{-1}		1 equiv. 0.14 mol L^{-1}		5 equiv. 0.70 mol L^{-1}	
	C / %	S / %	C / %	S / %	C / %	S / %	C / %	S / %
1	16.8	60.5	28.1	69.9	100.0	47.0	73.0	71.9
2	22.4	74.0	67.5	70.5	87.8	66.0	83.0	61.2
3	23.6	78.4	36.8	60.3	100.0	44.3	93.9	49.6
4	24.0	73.2	34.3	69.7	98.7	25.7	100.0	70.0
20	25.7	78.1	35.3	60.6	100.0	8.8	100.0	15.1

Table 4. Methyl ester **II** (methyl ferulate) conversion (C) and selectivity (S) toward dihydrobenzofuran neolignan (DBN) **2** as a function of the Ag_2O amount

Reaction time / h	0.25 equiv. 0.035 mol L^{-1}		0.5 equiv. 0.07 mol L^{-1}		1 equiv. 0.14 mol L^{-1}		5 equiv. 0.70 mol L^{-1}	
	C / %	S / %	C / %	S / %	C / %	S / %	C / %	S / %
1	21.7	57.9	31.3	75.0	74.1	33.0	95.4	15.9
2	25.0	55.4	39.4	66.3	44.8	43.2	93.8	16.0
3	25.1	65.0	45.8	55.8	49.0	43.5	92.4	11.1
4	28.6	53.6	44.4	63.1	95.1	25.6	97.7	20.8
20	27.1	66.9	46.5	69.2	94.2	13.0	100.0	11.0

Optimization of the solvent

Several solvents have been used in oxidative coupling reactions of phenylpropanoids. Dichloromethane and benzene/acetone and dichloromethane mixtures have been reported most often. Here, besides these two solvent systems, we also tested methanol and acetonitrile. The choice of these solvents was made on the basis of substrate solubility and the fact that methanol and acetonitrile are relatively "greener" as compared to other solvents: they present decreased toxicity and can be recycled for use in other reactions more times than other solvents.[21] In these experiments, we dissolved 1 equiv. of the substrate (methyl ester **I** or **II**) in 2 mL of the tested solvent and added the resulting solution to a 10-mL two-neck flask containing 0.5 equiv. of Ag_2O or $AgCO_2CF_3$, the two best oxidant agents for this reaction. We covered the reaction vessel with aluminum foil and kept the reaction mixture under stirring and N_2 atmosphere. The results are listed in Tables 5, 6, 7, and 8.

In acetonitrile (Sigma-Aldrich, St. Louis, USA), the reactions proceeded with good yields and increased selectivity as compared to the other solvents. Silver(I) produces diverse complexes with weak coordinating ligands (e.g., halogens), besides being weakly oxophilic and forming numerous complexes with donor groups, such as S, Se, P, As, and N donor ligands.[22] The increase in silver(I) valence due to formation of a complex when it is dissolved in cyanide solvents has been previously reported.[23] In this sense, the increased selectivity and good conversion rate of the substrates obtained here suggested that acetonitrile, which is a good electron donor, can form highly stable complexes with silver(I) during the oxidation. Both oxidants provided higher selectivity toward the DBNs **1** and **2**. Therefore, acetonitrile, which has not been previously reported as solvent for this reaction, is the best solvent to be used with Ag_2O, which in turn provides much more expressive results as compared to $AgCO_2CF_3$.

Optimization of the temperature

We also evaluated how the temperature influences the oxidative coupling of methyl esters **I** and **II**. Usually, these reactions are reported[2,19] to occur at room temperature. However, Sako *et al.*[20] obtained viniferin in 40% yield when they conducted AgOAc-promoted oxidative coupling in methanol under heating at 50 °C for 2 h. Here, we investigated how three different temperatures (0 °C, room temperature, and reflux at 85 °C) affected the oxidative coupling of methyl esters **I** and **II** by using Ag_2O, as oxidant, and acetonitrile, the best solvent for these reactions (Table 9).

Table 5. Methyl ester **I** (methyl *p*-coumarate) conversion (C) and selectivity (S) toward dihydrobenzofuran neolignan (DBN) **1** when Ag_2O (0.5 equiv.) is used as oxidant in different solvents

Reaction time / h	DCM		Benzene/acetone 6:4 (v/v)		MeOH		MeCN	
	C / %	S / %	C / %	S / %	C / %	S / %	C / %	S / %
1	5.5	34.5	5.2	41.7	5.8	28.4	26.2	60.7
2	7.1	50.4	10.0	55.5	8.6	36.6	35.0	62.7
3	15.5	37.4	14.7	59.7	13.0	38.3	36.8	60.3
4	15.3	63.8	12.7	57.2	12.7	43.7	34.3	69.6
20	27.5	73.0	35.3	66.4	30.2	51.0	35.3	60.6

DCM: dichloromethane; MeOH: methanol; MeCN: acetonitrile.

Table 6. Methyl ester **II** (methyl ferulate) conversion (C) and selectivity (S) toward dihydrobenzofuran neolignan (DBN) **2** when Ag_2O (0.5 equiv.) is used as oxidant in different solvents

Reaction time / h	DCM		Benzene/acetone 6:4 (v/v)		MeOH		MeCN	
	C / %	S / %	C / %	S / %	C / %	S / %	C / %	S / %
1	19.1	71.6	24.2	65.0	30.6	56.0	18.6	71.1
2	40.1	44.4	27.6	62.4	44.6	55.0	32.6	69.6
3	45.1	37.6	33.0	61.3	49.6	46.0	37.0	64.9
4	44.7	38.5	31.8	58.1	54.7	41.7	39.1	69.1
20	49.5	37.1	38.6	53.3	60.5	11.9	45.0	67.5

DCM: dichloromethane; MeOH: methanol; MeCN: acetonitrile.

Table 7. Methyl ester **I** (methyl *p*-coumarate) conversion (C) and selectivity (S) toward dihydrobenzofuran neolignan (DBN) **1** when $AgCO_2CF_3$ (0.5 equiv.) is used as oxidant in different solvents

Reaction time / h	DCM		Benzene/acetone 6:4 (v/v)		MeOH		MeCN	
	C / %	S / %	C / %	S / %	C / %	S / %	C / %	S / %
1	3.6	30.6	8.1	50.8	4.4	46.9	7.7	52.1
2	7.5	45.4	10.5	55.3	9.6	63.6	4.7	56.6
3	6.2	14.7	10.3	57.2	8.6	61.7	8.4	72.8
4	9.0	45.1	10.6	53.8	10.2	70.9	11.6	72.6
20	3.9	48.5	10.3	55.8	9.2	65.8	10.4	65.9

DCM: dichloromethane; MeOH: methanol; MeCN: acetonitrile.

Table 8. Methyl ester **II** (methyl ferulate) conversion (C) and selectivity (S) toward dihydrobenzofuran neolignan (DBN) **2** when $AgCO_2CF_3$ (0.5 equiv.) is used as oxidant in different solvents

Reaction time / h	DCM		Benzene/acetone 6:4 (v/v)		MeOH		MeCN	
	C / %	S / %	C / %	S / %	C / %	S / %	C / %	S / %
1	1.8	13.2	13.9	51.2	15.0	56.5	18.9	70.2
2	4.5	23.2	13.6	49.4	15.8	56.2	14.7	61.4
3	6.8	27.8	22.8	42.5	20.2	46.5	17.2	59.7
4	7.0	30.0	15.3	37.6	16.2	35.3	17.2	55.6
20	24.0	43.1	15.9	41.6	30.2	29.7	7.9	48.0

DCM: dichloromethane; MeOH: methanol; MeCN: acetonitrile.

Table 9. Methyl ester **I** (methyl *p*-coumarate) and methyl ester **II** (methyl ferulate) conversion (C) and selectivity (S) toward dihydrobenzofuran neolignans (DBN) **1** and **2**, respectively, when Ag_2O (0.5 equiv.) was used as oxidant in acetonitrile at different temperatures

Reaction time / h	Room temperature				0 °C				Reflux			
	I		**II**		**I**		**II**		**I**		**II**	
	C / %	S / %	C / %	S / %	C / %	S / %	C / %	S / %	C / %	S / %	C / %	S / %
1	49.7	76.3	29.8	76.0	6.6	31.0	12.9	61.3	28.6	73.7	63.7	78.3
2	47.6	72.7	39.0	76.6	6.9	23.8	18.9	67.9	29.8	66.1	68.8	58.8
3	57.1	73.2	38.6	78.4	9.8	44.5	23.1	71.4	26.9	63.1	66.3	74.3
4	50.1	75.3	41.7	77.1	11.9	50.0	35.5	77.3	30.0	56.3	65.7	71.0
20	49.1	71.7	45.4	77.3	44.9	71.1	46.9	71.3	44.4	42.1	68.0	64.1

Both conversion and selectivity decreased at 0 °C for both methyl esters. On the other hand, reflux conditions provided better homogenization of the reaction mixture and gave good selectivity and conversion. However, reaction time of 20 h decreased selectivity probably because side reactions took place, to afford products other than the DBNs **1** and **2**.

Optimization of the reaction time

Pieters *et al.*[17] reported that the optimum time for the silver(I)-promoted oxidative coupling of methyl esters **I** and **II** and analogs is 20 h. Nevertheless, our results revealed that this time could be optimized to 4 h in acetonitrile and 0.5 equiv. of Ag_2O without decreasing conversion and selectivity. The disadvantages of longer reaction times include reduced selectivity due to formation of undesired products.

The reflux condition was the most efficient among the tested conditions, especially in the case of methyl ester **II** (Table 9). However, we selected room temperature as the most adequate temperature for this reaction because it requires less energy and provides higher selectivity than reflux conditions.

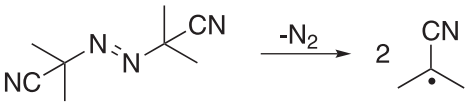
Table 10. Methyl ester **I** (methyl *p*-coumarate) and methyl ester **II** (methyl ferulate) conversion (C) and selectivity (S) toward dihydrobenzofuran neolignans (DBN) **1** and **2**, respectively, when Ag_2O (0.5 equiv., as oxidant) in acetonitrile at room temperature was used together with AIBN (radical initiator) or isoquinoline (radical inhibitor)

Reaction time / h	AIBN				Isoquinoline			
	I		**II**		**I**		**II**	
	C / %	S / %	C / %	S / %	C / %	S / %	C / %	S / %
1	80.0	5.7	70.2	7.1	57.9	49.1	38.1	35.0
2	87.6	5.8	73.8	8.2	60.1	46.5	45.6	41.2
3	85.8	6.1	76.9	7.0	60.5	47.7	43.7	41.5
4	88.8	5.6	78.3	6.4	60.2	45.7	47.8	39.0
20	86.3	5.6	78.6	10.1	62.5	47.1	48.6	40.1

AIBN: azobisisobutyronitrile.

Effect of radical initiator and inhibitor

AIBN (azobisisobutyronitrile) is a radical initiator due to its decomposition into 1-cyanoprop-1-yl radical, which is driven by N_2 elimination (Scheme 3).[24] AIBN has been used in many reactions in which radical intermediate species are involved.[25] Because the mechanism proposed in the literature[10,26] for the silver(I)-oxide oxidative coupling of phenylpropanoids involves the formation of radical intermediate species (Scheme 1), we decided to investigate how AIBN affected the synthesis of DBNs **1** and **2** from methyl esters **I** and **II**, respectively (Table 10). AIBN significantly increased methyl ester conversion in all the reaction times as compared to the reaction conducted under the same experimental conditions without AIBN addition. However, the selectivity toward DBNs **1** and **2** decreased drastically. This data indicated that AIBN addition to the reaction mixture generated other radical species that resulted in the formation of products other than the DBNs **1** and **2** even when the optimized conditions for oxidant, solvent, temperature, and reaction time were employed.



Scheme 3. Mechanism of 1-cyanoisoprop-1-yl radical formation from AIBN (adapted from reference 24).

Finally, we decided to verify how isoquinoline impacted the synthesis of DBNs **1** and **2** from methyl esters **I** and **II**, respectively. Isoquinoline acts as a radical inhibitor in organic synthesis.[27] Because the silver(I) oxide-promoted oxidative coupling of methyl esters **I** and **II** to produce **1** and **2**, respectively, has been suggested to involve intermediate radical species, we expected that isoquinoline addition would decrease the conversion of methyl esters **I** and **II** and the selectivity toward DBNs **1** and **2**, respectively. Surprisingly, although the selectivity decreased, the conversion of methyl esters **I** and **II** increased when isoquinoline was added. These results did not clarify the involvement of radical intermediate species in this reaction.

Conclusions

Silver(I) oxide (0.5 equiv.) is the most efficient oxidant amongst the silver(I) reagents that we tested to promote the oxidative coupling of methyl *p*-coumarate (**I**) and methyl ferulate (**II**) to produce the dihydrobenzofuran neolignans **1** and **2**. Acetonitrile, which has not been previously reported as solvent for this reaction, affords the best balance between conversion and selectivity, besides being "greener" than other more frequently employed solvents (e.g., dichloromethane and benzene). Under the optimized conditions, the reaction time can be reduced from 20 to 4 h without a significant decrease in conversion and selectivity. AIBN (a radical initiator) addition increases conversion and decreases selectivity, whereas isoquinoline (a radical inhibitor) addition slightly decreases reactivity and increases selectivity. The results of the experiments involving radical inhibitors/initiators to prove the involvement of radical intermediate species in the silver(I)-promoted oxidative coupling of the methyl esters **I** and **II** are not conclusive and must be investigated by other correlated experiments (e.g., mass spectrometry).

Supplementary Information

Supplementary information (IR, ^1H and ^{13}C NMR, and EI-MS spectra) is available free of charge at http://jbcs.sbq.org.br as PDF file.

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