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Synthesis of Pterocarpan-Type Heterocycles via Oxidative Cycloadditions of Phenols and Electron-Rich Arenes

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Synthesis of Pterocarpan-Type Heterocycles via Oxidative Cycloadditions of Phenols and Electron-Rich Arenes

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Abstract: Oxidation of 4-alkoxyphenols or 4-methoxynaphthol with phenyl iodonium(bis)trifluoroacetate (PIFA) in the presence of electron rich 2H-chromenes or dihydronaphthalenes affords pterocarpans or 5-carbapterocarpans via a formal [3 + 2] cycloaddition process. Acid-catalyzed ionization of quinone dimethylmonoacetal in the presence of 7-methoxy-2H-chromene gave similar results, suggesting a phenoxonium ion intermediate in the oxidative process.

Keywords: Carbapterocarpan, cycloaddition, hypervalent iodine reagent, oxidation, phenol, pterocarpan, quinone monoacetal

INTRODUCTION

Pterocarpans are members of a large family of widely distributed isoflavanoids produced by plants in response to fungal infections.[1] Interest in these polyoxygenated heterocycles stems from their unusal *cis*-fused dihydrobenzofuran–benzopyran ring juncture (Fig. 1) and a spectrum of biological properties including COX-2 inhibition,[2] and antitumor,[3] LDL-antioxidant,[4] anti-HIV,[5] and anti–snake venom activities.[6] A number of synthetic approaches have been reported over the years, many of which are multistep and proceed in poor overall

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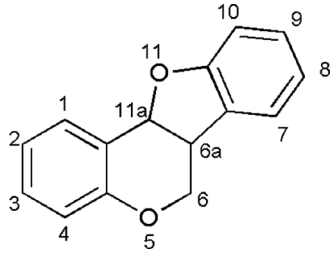


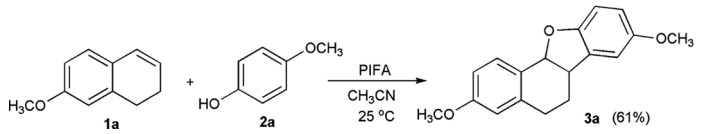
Figure 1. Numbering for pterocarpan ring system.

yield.[7c] Heck oxyarylation[8] and Ti(IV)-mediated benzoquinone cycloadditions with 2*H*-chromenes[9] have been widely employed, though both can give rise to structurally rearranged products in addition to the requisite *cis*-fused pterocarpan skeleton.

Oxidation of phenols with hypervalent iodine reagents in the presence of electron-rich styrenes has been shown to provide ready access to a number of dihydrobenzofuran structures in reasonable yield via a formal [3 + 2] cycloaddition process.[10] We report herein the use of 2*H*-chromenes and dihydronaphthalenes as nucleophilic arene components in such oxidative cycloadditions, leading to rapid and convergent assembly of several novel pterocarpan-type ring systems in a single step from readily available phenols under mild conditions.

RESULTS AND DISCUSSION

7-Methoxy-1,2-dihydronaphthalene (**1a**) and chromenes **1b** and **1c** for the study (Table 1) were prepared by literature methods.[11] Initial chemical oxidation of an equimolar mixture of **1a** and 4-methoxyphenol (**2a**) in MeCN with phenyl iodonium (bis)trifluoroacetate (PIFA) (1 equiv) at room temperature for 15 min followed by standard workup and chromatographic isolation gave a product whose ^{1}H and ^{13}C NMR data were consistent with formation of the corresponding 5-carbapterocarpan cycloadduct **3a** in 61% isolated yield (Entry 1, Table 1).



(1)

In multiple trials, no improvement in yield of **3a** was obtained through use of an excess of **1a** and **2a** or the oxidant. This stands in

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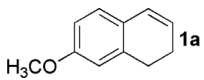
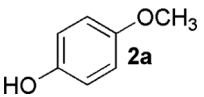
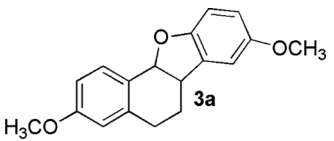
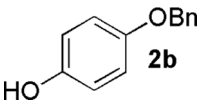
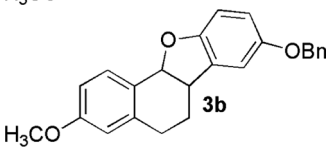
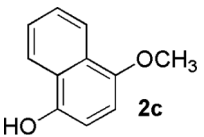
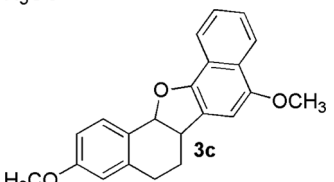
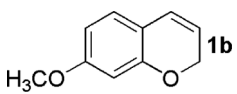
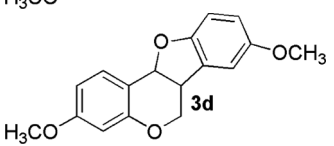
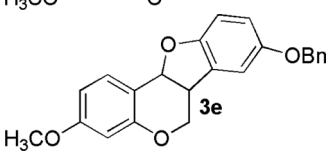
Table 1. Pterocarpan-type heterocycles via oxidative cycloadditions of phenols and arenas

Entry	Arene 1	Arene 2	Product 3	Yield (%)
1	 **1a**	 **2a**	 **3a**	61
2	**1a**	 **2b**	 **3b**	50
3	**1a**	 **2c**	 **3c**	40
4	 **1b**	**2a**	 **3d**	49
5	**1b**	**2b**	 **3e**	47

(*Continued*)

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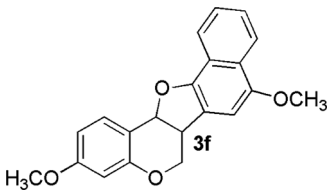
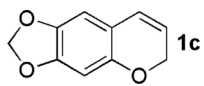
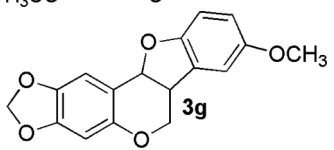
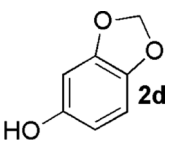
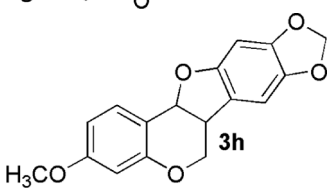
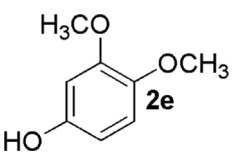
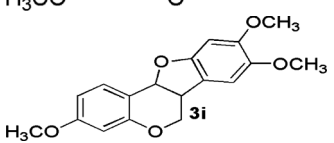
Table 1. Continued

Entry	Arene 1	Arene 2	Product 3	Yield (%)
6	**1b**	**2c**		62
7		**2a**		49
8	**1b**			17
9	**1b**			2

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contrast to the 5:1 styrene-to-phenol molar ratio reportedly required for optimal yields in similar oxidative cycloadditions, leading to dihydrobenzofurans.[10] As shown in Table 1, yields of other cycloadducts **3** were reasonable only when the phenolic component possessed alkoxyl substitution solely at the *para*-position. Thus, oxidation of phenols **2a** and **2b** or 4-methoxynaphthol (**2c**) in the presence of **1a** (entries 1–3) or **1b** (entries 4–6) gave, respectively, 5-carbapterocarpans **3a**–**c** and pterocarpans **3d**–**f** in comparable yields (47–62%). Additional oxygenation at position 2 of the chromene ring, as in **1c**, gave similar results (entry 7). However, *sesamol* **(2d)**, when oxidized in the presence of **1b**, led to a disappointingly poor yield of naturally occurring (±)-*pterocarpin* **(3 h)** (entry 8), whereas oxidation of 3,4-dimethoxyphenol (**2e**) in the presence of **1b** led to a complex mixture containing only a small amount of impure cycloadduct **3i** (entry 9). Similar oxidation using 3-methoxyphenol gave no recoverable product. Because oxygenation at position 9 is common to most naturally occuring pterocarpans, these latter results represent an important limitation of the chemistry.

Structure assignments for cycloadducts **3** were supported by comparison of ^{1}H and ^{13}C NMR and/or melting-point (mp) data with literature values (**3d, h**) as well as by elemental analysis for new compounds (**3a**–**c, 3e**–**g**). The expected *cis*-fused pterocarpan ring junction was also confirmed by single-crystal x-ray analysis of **3d** (Fig. 2).

For the reactions leading to **3 h** and **3i**, mostly unreacted **1b** was recovered after chromatography, which argued against competing oxidation of products (in spite of their additional oxygenation) as a cause for poor yields. Nevertheless, because **3 h** was rapidly consumed when treated alone with excess PIFA in MeCN, we briefly examined nonoxidative methods for generating the phenoxonium ions presumably involved in these cycloadditions. Thus, stirring of a solution of quinone monoacetal **4a** and chromene **1b** in MeCN in the presence of acidic montmorillonite

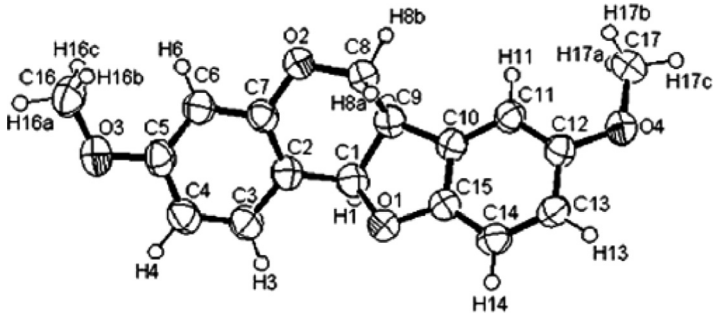
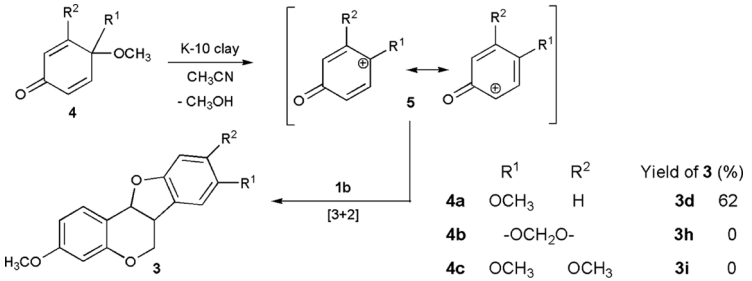


Figure 2. Ortep diagram for **3d**.



Scheme 1. Synthesis of **3d** via nonoxidative cycloaddition.

K-10 clay led to formation of pterocarpan **3d** in 62% yield, comparable to that obtained via PIFA oxidation of phenol **2a** (Scheme 1). This supported the hypothesis that phenoxonium ions **5** were likely intermediates in the oxidative cycloaddition process. However, reaction of **1b** with quinone monoacetals **4b** or **4c**[12] under the same conditions of acid catalysis gave no recoverable amount of the corresponding pterocarpan cycloadducts. Although no further studies were done, these results suggested that poor yields of cycloadducts from phenols **2d** or **2e** via the oxidative method may have been due to an inherent instability of the corresponding phenoxonium ions.

CONCLUSIONS

Pterocarpan-type structures may be prepared in a single step in reasonable yield via oxidation of 4-alkoxyphenols or naphthols with PIFA in the presence of electron-rich chromenes or dihydronaphthalenes in acetonitrile solution at room temperature.

EXPERIMENTAL

All NMR spectra were recorded at 300 MHz (^{1}H) and 125 MHz (^{13}C) on a Bruker Avance spectrometer and were measured in deuteriochloroform with tetramethylsilane (TMS) as internal standard. Signals are reported in δ values (ppm) downfield from TMS. Melting points were determined in open capillary tubes on a Thomas-Hoover apparatus and are uncorrected. Elemental analyses were provided by Galbraith Laboratories, Knoxville, TN. Compounds **1a**–**c** and **4a**–**c** were prepared following previously published procedures.[11,12] All other compounds and reagents were obtained from the Aldrich Chemical Co.

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General Procedure for Oxidative Cycloadditions

Solid PIFA (1.8 mmol) was added to an equimolar mixture of the requisite phenol (1.8 mmol) and chromene or dihydronaphthalene (1.8 mmol) in CH_3CN (5 mL) all at once. After stirring 15 min, the reaction was quenched with sat. $NaHCO_3$(2 mL). Ether (25 mL) was added, the layers were separated, and the organic phase was extracted with brine (2×10 mL), dried over anhydrous $CaSO_4$, and concentrated in vacuo. Chromatography of the residue on silica gel (10% EtOAc–hexane) afforded the indicated cycloadducts **3a**–**i** as crystalline solids.

Data

(±)-5-Carba-3,8-dimethoxypterocarpan **3a**

Yield: 0.310 g (61%); mp 89–91°C; ^{1}H NMR: δ 1.78–1.87 (m, 1 H), 1.97–2.04 (m, 1 H), 2.60–2.69 (m, 2 H), 3.56–3.63 (m, 1 H), 3.76 (s, 3 H), 3.78 (s, 3 H), 5.61 (d, $J = 8.3$ Hz, 1 H), 6.65–6.69 (m, 3 H), 6.81–6.84 (m, 2 H), 7.43 (d, $J = 8.2$ Hz, 1 H); ^{13}C NMR: δ 27.91, 27.92, 41.57, 55.30, 56.02, 81.96, 109.41, 110.78, 112.64, 112.89, 113.30, 125.86, 131.47, 132.54, 140.45, 153.50, 154.17, 159.41. Anal. calcd. for $C_{18}H_{18}O_3$: C, 76.57; H, 6.43. Found: C, 76.70; H, 6.54.

(±)-8-Benzyloxy-5-carba-3-methoxypterocarpan **3b**

Yield: 0.322 g (50%); mp 101.5–103°C; ^{1}H NMR: δ 1.75–1.88 (m, 1 H), 1.95–2.10 (m, 1 H), 2.58–2.80 (m, 2 H), 3.60–3.70 (m, 1 H), 3.80 (s, 3 H), 5.01 (s, 2 H), 5.63 (d, $J = 8.4$ Hz, 1 H), 6.67–6.78 (m, 3 H), 6.86 (dd, $J = 8.4$ Hz, $J = 2.6$ Hz, 1 H) 6.91 (d $J = 2.6$ Hz, 1 H), 7.31–7.49 (m, 6 H); ^{13}C NMR: δ 27.87, 27.88, 41.53, 55.31, 71.08, 81.99, 109.43, 111.97, 112.63, 113.30, 114.14, 125.84, 127.61 (2C), 127.94, 128.59 (2C), 131.46, 132.50, 137.38, 140.45, 153.37, 153.73, 159.40. Anal. calcd. for $C_{24}H_{22}O_3$: C, 80.42; H, 6.19. Found: C, 80.57; H, 6.23.

(±)-9,10-Benzo-5-carba-3,8-dimethoxypterocarpan **3c**

Yield: 0.239 g (40%); mp 127–129°C; ^{1}H NMR: δ 1.82–1.98 (m, 1 H), 2.03–2.17 (m, 1 H), 2.57–2.78 (m, 2 H), 3.81 (s, 3 H), 3.80–3.85 (m, 1 H), 3.99 (s, 3 H), 5.82 (d, $J = 8.7$ Hz, 1 H), 6.69 (d, $J = 2.3$ Hz, 1 H), 6.78 (s, 1 H), 6.88 (dd, $J = 8.4$ Hz, $J = 2.5$ Hz, 1 H), 7.39–7.43 (m, 2 H), 7.56 (d, $J = 8.4$ Hz, 1 H), 7.87–7.89 (m, 1 H), 8.16–8.19 (m, 1 H);

^{13}C NMR: δ 27.86, 28.03, 42.64, 55.29, 56.10, 82.13, 100.98, 112.43, 113.29, 121.56, 122.36, 122.76, 124.98, 125.51, 125.84, 126.24, 131.58, 140.90, 148.61, 150.13, 159.41, 166.17. Anal. calcd. for $C_{22}H_{20}O_3$: C, 79.50; H, 6.06. Found: C, 79.74; H, 6.06.

(±)-3,8-Dimethoxypterocarpan **3d**

Yield: 0.251 g (49%); mp 118–119°C (lit.[13] mp 115–116°C); ^{1}H NMR: δ 3.55–3.66 (m, 1 H), 3.73 (t, $J = 10.9$ Hz, 1 H), 3.78 (s, 3 H), 3.79 (s, 3 H), 4.27 (dd, $J = 10.9$ Hz, $J = 5.0$ Hz, 1 H), 5.48 (d, $J = 6.7$ Hz, 1 H), 6.46 (d, $J = 2.5$ Hz, 1 H), 6.63 (dd, $J = 8.5$ Hz, $J = 2.5$ Hz, 1 H), 6.67–6.80 (m, 2 H), 6.83 (d, $J = 2.5$ Hz, 1 H), 7.41 (d, $J = 8.6$ Hz, 1 H); ^{13}C NMR: δ 40.61, 55.39, 56.02, 66.23, 77.84, 101.61, 109.19, 110.15, 111.10, 112.37, 113.85, 128.10, 131.84, 153.37, 154.32, 156.50, 161.02.

(±)-8-Benzyloxy-3-methoxypterocarpan **3e**

Yield: (0.305 g (47%); mp 135–136°C; ^{1}H NMR: δ 3.59–3.53 (m, 1 H), 3.69 (t, $J = 10.9$ Hz, 1 H), 3.80 (s, 3 H), 4.25 (dd, $J = 10.9$ Hz, $J = 4.6$ Hz, Hz, 1 H), 5.01 (s, 2 H), 5.48 (d, $J = 6.7$ Hz, 1 H), 6.47 (d, $J = 2.5$ Hz, 1 H), 6.64 (dd, $J = 8.5$ Hz, $J = 2.5$ Hz, 1 H), 6.74–6.82 (m, 2 H), 6.91 (d, $J = 2.5$ Hz, 1 H), 7.33–7.45 (m, 6 H); ^{13}C NMR: δ 40.61, 55.38, 66.23, 71.09, 77.88, 101.64, 109.20, 110.16, 112.31, 112.38, 115.11, 127.53 (2C), 127.96, 128.11, 128.58, 131.84 (2C), 137.20, 153.53, 153.63, 156.53, 161.04. HRMS m/z 360.1367; calcd. for $C_{23}H_{20}O_4$ 360.1362.

(±)-9,10-Benzo-3,8-dimethoxypterocarpan **3f**

Yield: 0.373 g (62%); mp 163–164.5°C; ^{1}H NMR: δ 3.80 (s, 3 H), 3.83–3.73 (m, 2 H), 3.99 (s, 3 H), 4.37 (dd, $J = 9.6$ Hz, $J = 3.6$ Hz, 1 H), 5.67 (d, $J = 6.6$ Hz, 1 H), 6.49 (d, $J = 2.5$ Hz, 1 H), 6.69 (dd, $J = 8.5$ Hz, $J = 2.5$ Hz, 1 H), 6.77 (s, 1 H), 7.43–7.48 (m, 2 H), 7.56 (d, $J = 8.5$ Hz, 1 H), 7.94 (dd, $J = 6.1$ Hz, $J = 2.3$ Hz, 1 H), 8.20 (dd, $J = 7.2$ Hz, $J = 1.1$ Hz, 1 H); ^{13}C NMR: δ 41.71, 55.40, 56.06, 66.66, 78.07, 100.63, 101.66, 109.19, 112.80, 118.93, 121.51, 121.25, 122.53, 125.45, 125.89, 126.18, 132.03, 148.95, 150.36, 156.70, 161.02. Anal. calcd. for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.81; H, 5.49.

(±)-8-Methoxy-3,4-methylenedioxypterocarpan **3g**

Yield: 0.263 g (49%); mp 161–163°C; ^{1}H NMR: δ 3.54–3.67 (m, 2 H), 3.77 (s, 3 H), 4.23 (dd, $J = 10.5$ Hz, $J = 4.3$ Hz, 1 H), 5.42 (d, $J = 6.7$ Hz, 1 H),

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5.86, (dd, $J = 9.2$, 1.1 Hz, 2 H), 6.46 (s, 1 H), 6.69–6.76 (m, 2 H), 6.83 (d, $J = 2.4$ Hz, 1 H), 6.93 (s, 1 H); ^{13}C NMR: δ 40.63, 56.01, 66.46, 78.22, 98.85, 101.29, 108.79, 110.10, 111.09, 111.94, 113.88, 127.94, 142.60, 148.76, 150.85, 153.20, 154.35. Anal. calcd. for $C_{17}H_{14}O_5$: C, 68.45; H, 4.73. Found: C, 68.22; H, 4.69.

(±)-3-Methoxy-8,9-methylenedioxypterocarpan **3h** ((±)-pterocarpin)

Yield: 0.091 g (17%); mp 183–185°C (lit. mp 168–169°C[14a] and 185–186°C[14b]); ^{1}H NMR: δ 3.48–3.52 (m, 1 H), 3.66 (t, $J = 10.9$ Hz, 1 H), 3.79 (s, 3 H), 4.23 (dd, $J = 10.9$ Hz, $J = 4.9$ Hz, 1 H), 5.49 (d, $J = 6.9$ Hz, 1 H), 5.90 (dd, $J = 8.6$ Hz, $J = 1.3$ Hz, 2 H), 6.43 (s, 1 H), 6.47 (d, $J =$ 2.5 Hz, 1 H), 6.64 (dd, $J = 8.5$ Hz, $J = 2.5$ Hz, 1 H), 6.72 (s, 1 H), 7.40 (d, $J = 8.6$ Hz, 1 H); ^{13}C NMR: δ 40.20, 55.38, 66.50, 78.50, 93.83, 101.29, 101.63, 104.73, 109.17, 112.34, 117.94, 131.75, 141.70, 148.09, 154.27, 156.58, 161.05.

(±)-3,8-Dimethoxypterocarpan **3d** via Nonoxidative Cycloaddition

Powdered montmorillonite K-10 clay (0.050 g) was added to a solution of 7-methoxy-2*H*-chromene **1b** (0.090 g, 0.56 mmol) and quinone dimethylmonoacetal **4a** (0.043 g, 0.28 mmol) in dry CH_3CN (2 mL), and the resulting suspension was stirred for 15 min. Concentration in vacuo and chromatography of the residue on silica gel (10% EtOAc/hexane) afforded **3d** (0.050 g, 62% based on **4a**).

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