A New Method for the Preparation of Aryl Vinyl Ethers

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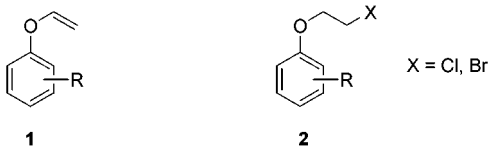
Introduction

Vinyl ethers are valuable chemical entities that can be used in a wide array of chemical transformations.[1] More specifically, aryl vinyl ethers of the general structure **1**, where the vinyl moiety is unsubstituted, have been involved in reactions such as [2 + 2],[2,3] [4 + 2],[4,5] and 1,3-dipolar cycloadditions,[6] cyclopropanations,[7] and hydroformylations.[8] Under acidic conditions, they react with alcohols[9] to give acetals that can act as protecting groups.[9a]

Aryl vinyl ethers of the structure **1** are generally prepared according to either of the following methods: the addition of phenols to acetylene[10] and the dehydrohalogenation of aryl 2-haloethyl ethers (**2**).[11] Both procedures require strong bases and elevated temperatures. Low to moderate yields of aryl vinyl ethers are usually obtained and such reactions conditions are unsuitable for sensitive substrates. Even considering the improvements brought by Mizuno et al. to the second of these processes,[11a] the discovery of a mild method to prepare aryl vinyl ethers of type **1** is highly desirable.

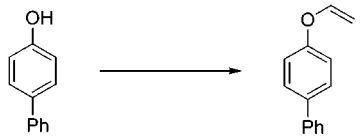


1 **2**

Recently, Evans published a procedure for the synthesis of diaryl ethers involving a mild copper(II)-promoted coupling of arylboronic acids and phenols.[12] A logical extension to aryl vinyl ethers of type **1** would be to couple phenols with vinylboronic acid, but unfortunately this acid is not very stable.[13] In their report, Evans et al. mention that aryltrialkylstannanes also participate in this transformation, albeit in lower yields compared to arylboronic acids. Herein, we report a mild and efficient copper(II)-promoted conversion of phenols to aryl vinyl ethers, in a single step, using tetravinyltin as the vinylating agent.

Results and Discussion

We submitted 4-phenylphenol (**3a**) to Evans's reaction conditions [$Cu(OAc)_2$ (1.0 equiv), Et_3N (5.0 equiv), powdered 4 Å molecular sieves, CH_2Cl_2 (0.1 M in phenol), room temperature, air exposure] using commercially available tributyl(vinyl)tin (1.5 equiv) as the vinylating agent. After 4 days, a filtration workup and chromatography afforded the desired vinyl ether **1a** in a 22% yield, slightly contaminated with tin-containing residues. In attempts to optimize this reaction, only the use of acetonitrile as the solvent instead of dichloromethane had a beneficial effect, bringing up the yield to 41%.



3a **1a**

Our investigations took a sharp turn when we decided to substitute tetravinyltin for tributyl(vinyl)tin. This reagent, in the same conditions, using CH_3CN as the

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(1) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 9, Cumulative Indexes. See enol ethers; ethers, phenyl vinyl; ethers, vinyl; vinyl ethers.

(2) For selected examples of [2 + 2] cycloadditions, see: (a) El-Nabi, H. A. A. *Tetrahedron* **1997**, *53*, 1813. (b) Griesbeck, A. G.; Stadtmüller, S.; Busse, H.; Bringmann, G.; Buddrus, J. *Chem. Ber.* **1992**, *125*, 933. (c) Brückner, R.; Huisgen, R. *Tetrahedron Lett.* **1990**, *31*, 2557.

(3) For selected examples of hetero [2 + 2] cycloadditions, see: (a) Futamura, S.; Ohta, H.; Kamiya, Y. *Bull. Chem. Soc. Jpn.* **1982**, *55*, 2190. (b) Firl, J.; Sommer, S. *Tetrahedron Lett.* **1970**, *11*, 1929.

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(5) For selected examples of hetero Diels−Alder reactions, see: (a) Wada, E.; Yasuoka, H.; Kanemasa, S. *Chem. Lett.* **1994**, 145. (b) Hojo, M.; Masuda, R.; Okada, E. *Synthesis* **1990**, 347.

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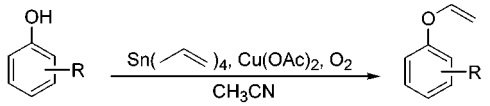
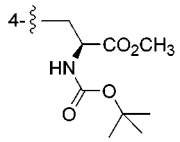
Table 1. Preparation of Aryl Vinyl Ethers 1a–j from Phenols 3a–j



3a-j **1a-j**

Entry	Phenol	R	Product	Temperature (Time)	Yield, %[a]
1	**3a**	4-Ph	**1a**	rt (22 h)	93
2	**3b**	3-Ph	**1b**	rt (22 h)	94
3	**3c**	2-Ph	**1c**	rt (22 h)	93
4	**3d**	4-OC_6H_{13}	**1d**	rt (6 h)	89
5	**3e**	4-Br	**1e**	rt (22 h)	83
6	**3f**	4-CN	**1f**	60 °C (19 h)	48
7	**3g**	4-NO_2	**1g**	60 °C (19 h)	50
8	**3h**	4-CO_2CH_3	**1h**	rt (96 h)	90
9	**3i**	4-$NHCOCH_3$	**1i**	rt (22 h)	96
10	**3j**[b]		**1j**[c]	rt (22 h)	92

[a] Isolated yield after purification. [b] $[\alpha]^{22}_D$ +51 (c = 1, $CHCl_3$). [c] $[\alpha]^{22}_D$ +55 (c = 1, $CHCl_3$).

solvent, afforded the desired aryl vinyl ether **1a** in 74% yield. Control experiments revealed that while oxygen is necessary for high conversion, molecular sieves and triethylamine are not. Thus, under optimized conditions, when phenol **3a** was treated with tetravinyltin (1.2 equiv), in the presence of $Cu(OAc)_2$ (1.2 equiv), in CH_3CN (0.3 M) and under an atmosphere of pure O_2,[14] the vinyl ether **1a** was isolated in 93% yield after an aqueous workup and chromatography.

Even though tetravinyltin could potentially deliver more than one vinyl unit per mole, at least 1 equiv is needed to achieve a >90% conversion to **1a**.[15] In addition, we demonstrated that this process could not be run under catalytic copper(II) conditions.[16] $Cu(OAc)_2$ was found to be the best copper promoter for this transformation. Copper powder, $CuCl_2$, $Cu(TFA)_2$, and CuOAc allowed conversions of 5, 10, 50, and 90%, respectively. Other divalent transition metals, such as Ni(II), Pd(II), and Hg(II) did not promote the reaction.

To evaluate the scope of this transformation, a variety of phenols, with different substitution patterns, were subjected to the reaction conditions. The results are outlined in Table 1. The reaction seems insensitive to proximal substitution. Isomeric 3-phenyl (**3b**) and 2-phenylphenol (**3c**) (entries 2 and 3) were converted to their respective vinyl ethers **1b** and **1c** in yields essentially identical to their *para* analogue **3a** (entry 1). Similar results were observed with a substrate bearing an electron-donating group (EDG), as *p*-hexyloxyphenyl vinyl ether (**1d**) was obtained in 89% isolated yield (entry 4). Such a substituent increases the reaction rate. On the other hand, electron-withdrawing groups (EWG) decrease the rate, as illustrated by entries 5–8. While the weak 4-bromo EWG did not affect the transformation (entry 5), 4-cyanophenol (**3f**) and 4-nitrophenol (**3g**) required a temperature increase (60 °C) to be vinylated. The yield of their respective products **1f** and **1g** is also lower (entries 6 and 7). A mild EWG, such as carbomethoxy, had a moderate effect. Heat was not necessary for the reaction to proceed, but more time (96 h) was needed to reach maximum conversion (entry 8). An acetamido group in the *para* position had no effect on the reaction (entry 9). The mildness of this vinylating process is clearly demonstrated with entry 10, as the vinyl derivative of BOC-protected L-tyrosine methyl ester (**1j**) was prepared in 92% isolated yield without racemization.

Hydroxylated heterocycles such as hydroxypyridines and hydroxyquinolines can be vinylated under the conditions reported herein. While 4-hydroxypyridine (**7a**) and 2-hydroxyquinoline (**7b**) were selectively *N*-vinylated,[17] 6-hydroxyquinoline (**7c**) was *O*-vinylated[18] (Table 2).

A possible mechanism for the reaction, analogous to one proposed for the diaryl ether formation,[12] is outlined in Scheme 1. The attack of the phenol on the vinylcopper species **4** could lead to vinylcopper(II) phenoxide **5**. The

(14) A similar yield can be obtained upon exposure to ambient atmosphere, but the transformation is slower.

(15) When **3a** was treated with tetravinyltin (0.5 equiv) and $Cu(OAc)_2$ (1.0 equiv), 80% conversion to **1a** was measured at 48 h (^{1}H NMR spectrum of crude product).

(16) 40% conversion (^{1}H NMR spectrum of crude product) of **3a** to **1a** was observed when 1.5 equiv and 0.3 equiv of tetravinyltin and $Cu(OAc)_2$ respectively, were used.

Scheme 1

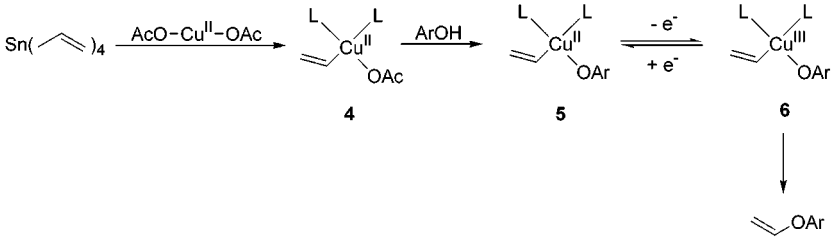
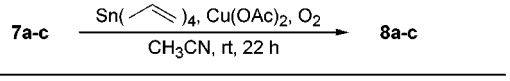
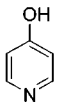
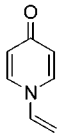
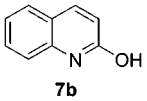
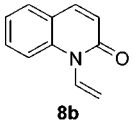
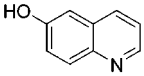
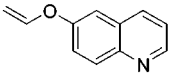


Table 2. Vinylation of Hydroxylated Heterocycles 7a−c



Entry	Het-OH	Product	Yield, %[a]
1	 **7a**	 **8a**	60[b]
2	 **7b**	 **8b**	97
3	 **7c**	 **8c**	66[c]

[a] Isolated yield after purification. [b] No workup (**8a** is water soluble); reaction stopped with 3 drops of concentrated NH_4OH (10 min), mixture directly applied on column for chromatography. [c] Reaction stopped with 1 mL of concentrated NH_4OH (10 min), then 25% NH_4OAc added and usual workup.

latter could subsequently be oxidized, through the action of oxygen, to the copper(III) intermediate **6** prior to reductive elimination to the vinyl ether product. Most likely, the solvent (CH_3CN) acts as ligand (L).

Conclusion

In summary, we have developed a mild, single-step procedure for the preparation of aryl vinyl ethers, through the copper(II)-promoted vinylation of phenols, with tetravinyltin, in acetonitrile and under an oxygen atmosphere. The reaction is applicable to a variety of phenolic substrates. In particular, sensitive molecules such as L-tyrosine derivative **3j**, impossible to vinylate by current methods, can be obtained in high yield via this new procedure.

Experimental Section

General. ^1H NMR spectra were recorded at 400 or 500 MHz in acetone-d_6 or $CDCl_3$, using their respective signal for standardization. Broad band proton-decoupled ^{13}C NMR spectra were recorded at 125.8 MHz in $CDCl_3$, using $CDCl_3$ as internal standard. Anhydrous $Cu(OAc)_2$, tetravinyltin, and anhydrous CH_3CN were purchased from Aldrich. Flash chromatography was performed using 230−400 mesh silica gel and compound detection from analytical TLC plates was performed using UV light. FAB high-resolution mass spectra were run in glycerol at The Biomedical Mass Spectrometry Unit, McGill University, Montréal, Québec, Canada. Elemental analyses were performed at Le Laboratoire d'Analyse Élémentaire, Université de Montréal, Montréal, Québec, Canada.

Preparation of Aryl Vinyl Ethers 1a−j and Vinylated Heterocycles 8a−c. The procedure described below for the preparation of aryl vinyl ether **1a** is typical. Footnotes *b* and *c* of Table 2 indicate minor modifications in the workup for compounds **8a** and **8c**. Details regarding the purification of each compound appear in the Supporting Information. Only aryl vinyl ethers **1d** and **1j** are new compounds. They were fully characterized and their data appear in the Supporting Information. All the other vinyl ethers have been previously reported.[19] Although characterization data for compounds **1a−c**, **1e−i,** and **8a−c** are in agreement with those reported, they were also fully characterized, except for **1e** for which a satisfactory HRMS was not obtained (see the Supporting Information). Litterature data for these compounds were often found to be incomplete. Starting materials (**3a−j** and **7a−c**) are commercially available.

4-(Vinyloxy)-1,1′-biphenyl (1a). Anhydrous $Cu(OAc)_2$ (218 mg, 1.20 mmol) was added to a solution of 4-phenylphenol (**3a**) (170 mg, 1.00 mmol) in CH_3CN (3 mL). The mixture was purged under vacuum, and dry O_2 was introduced in the septum-capped flask, via a balloon fitted with a needle. Tetravinyltin (218 μL, 1.20 mmol) was then added to the turquoise mixture that subsequently faded (∼3 min) to a grayish color. After 22 h at room temperature, the resulting dark green mixture was poured into aqueous 25% NH_4OAc (25 mL). After 10 min of stirring, the blue aqueous layer was extracted with EtOAc (3×). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The gummy residue was subjected to column chromatography ($CHCl_3$/hexane 10:90), affording the vinyl ether **1a** as a white solid (182 mg, 93%): ^1H NMR (500 MHz, acetone-d_6) δ 4.47 (dd, J = 6.0, 1.5 Hz, 1H), 4.75 (dd, J = 13.6, 1.5 Hz, 1H), 6.85 (dd, J = 13.6, 6.0 Hz, 1H), 7.13 (m, 2H), 7.33 (m, 1H), 7.44 (m, 2H), 7.61−7.66 (m, 4H); ^{13}C NMR δ 95.4, 117.4, 126.9, 127.1, 128.4, 128.9, 136.2, 140.5, 148.1, 156.4; IR (KBr) 3050, 3020, 1635, 1595, 1510, 1475, 1240, 1135, 825, 755, 685 cm^{-1}; HRMS (FAB) calcd for $C_{14}H_{13}O$ (M + H)$^+$ 197.0966, found 197.0966. Anal. Calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.58; H, 6.24.

Supporting Information Available: Details on the purification and characterization data for compounds **1b−j** and **8a−c**; copies of ^1H NMR and ^{13}C NMR spectra for **1b−i** and **8a−c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) ^1H and ^{13}C NMR data obtained for **8a** and **8b** are in complete agreement with those reported. See: Afonin, A. V.; Andriyankov, M. A.; Pertsikov, B. Z.; Voronov, V. K. *Zh. Org. Khim.* **1986**, *22*, 2451.

(18) ^1H and ^{13}C NMR data obtained for **8c** are in complete agreement with those reported. See: Afonin, A. V.; Vashchenko, A. V.; Contreras, R. H. *Russ. J. Org. Chem.* **1997**, *33*, 1427; *Zh. Org. Khim.* **1997**, *33*, 1507.

(19) (a) For data on compounds **1a** and **1c**, see ref 10e. (b) For **1b**, see: Wagner, P. J.; Klán, P. *J. Am. Chem. Soc.* **1999**, *121*, 9626. (c) For **1e** and **1g**, see: Afonin, A. V.; Vashchenko, A. V.; Tagaki, T.; Kimura, A.; Fujiwara, H. *Can. J. Chem.* **1999**, *77*, 416. (d) For **1f** and **1h**, see: Bzhezovskii, V. M.; Finkel'shtein, B. L.; Kushnarev, D. F.; Kalabin, G. A.; Trofimov, B. A. *J. Org. Chem. USSR (Engl. Transl.)* **1990**, *26*, 15; *Zh. Org. Khim.* **1990**, *26*, 19. (e) For **1i**, see: Skvortsova, G. G.; Kurov, G. N.; Samoilova, M. Ya. *J. Org. Chem. USSR (Engl. Transl.)* **1966**, *2*, 1046; *Zh. Org. Khim.* **1966**, *2*, 1054. (f) For **8a**,**b**, see ref 17; (g) For **8c**, see ref 18.