Ortho-Vinylation and Ortho-Alkenylation of Phenols

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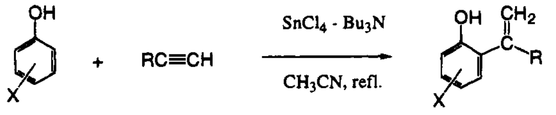
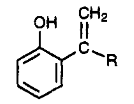
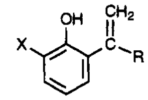
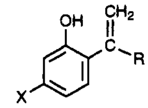
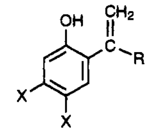
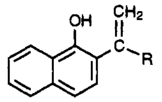
Direct vinylation of aromatic compounds is yet an unsolved problem in organic synthesis. Various undesired products are formed when aromatics are treated with vinyl halides or alkynes under electrophilic reaction conditions.[1,2] As for phenols, acid treatment with ethyne gave poly(vinylphenols)s.[3] Although *o*-(1-phenylethenyl)phenols were obtained from magnesium phenoxides and phenylacetylene, the reaction could be carried out only with this alkyne.[4] Condensation of acetone with phenols was used to prepare *o*-(2-propenyl)phenols.[5] However, the applicability of the method is inherently limited. *o*-Vinylphenols, therefore, were synthesized *via* decarboxylation of *o*-hydroxycinnamic acids.[6] We wish to describe here the direct ortho-vinylation and ortho-alkenylation of phenols with ethyne and 1-alkynes.

Reaction of 1-alkynes, phenols, $SnCl_4$, and Bu_3N in refluxing acetonitrile followed by aqueous workup gives ortho-alkenylphenols (Table 1). Both aliphatic and aromatic 1-alkynes react at the internal carbon atom, giving *exo*-olefins. There is no detectable double bond isomerization to the more stable trisubstituted olefin in acetonitrile, but it is serious side reaction in 1,2-dichloroethane or benzene. The C−C bond formation occurs at the ortho-position of the phenolic hydroxyl group. Meta-substituted phenols are alkenylated at the less hindered ortho-site. Attempted reaction of 2,6-dimethylphenol results in the recovery of the starting material, and no para-substitution is detected. Employment of approximately equimolar amounts of phenol and 1-alkyne gives satisfactory results, unless the phenol possesses an electron-withdrawing group. These unreactive aromatic compounds are alkenylated under relatively forcing conditions. Phenol and para-substituted phenol require use of 3 mol equiv of the $SnCl_4{-}Bu_3N$ reagent, giving monoalkenylated products selectively. A mixture of 2-alkenylphenol and 2,6-dialkenylphenol is formed when a reduced amount of the reagent (2 equiv) is used (see reactions of *p*-cresol). Functionalities such as ester, secondary amide, the dimethylamino group, and the (*tert*-butyldiphenylsilyl)oxy group are tolerated. It should be emphasized that the vinyl group can be introduced with gaseous ethyne (Scheme 1), which is the first example of direct vinylation of phenols. Interestingly, (trimethylsilyl)acetylene reacts at the terminal carbon atom, giving (*E*)-(β-(trimethylsilyl)phenols. The regioselectivity reverses from that observed for aliphatic and aromatic 1-alkynes. The vinylation and the β-(trimethylsilyl)ethenylation are conducted in 1,2-dichloroethane, since the reactions are sluggish

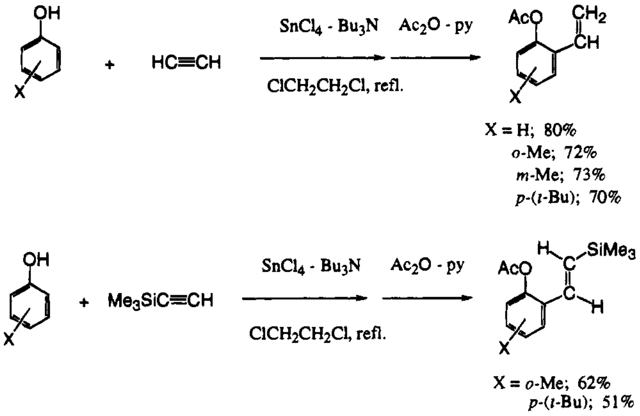
Table 1. Ortho-Alkenylation of Phenols with 1-Alkynes[a]



X	R	product	yield/%[b]
H	$Ph(CH_2)_2$		65/10[c]
	Ph		71/3[c]
o-Me	$Ph(CH_2)_2$		68
	m-$MeOC_6H_4$		78
m-Me	$Ph(CH_2)_2$		68
m-MeO	Ph		81
	n-C_5H_{11}		69
m-Me_2N	*n*-C_5H_{11}		73[d]
p-Me	$Ph(CH_2)_2$		28/25 62/8[c]
p-Ph	*n*-C_5H_{11}		67/9[c]
p-MeO	*n*-C_5H_{11}		74[c]
p-(*t*-BuCONH)	*t*-$BuPh_2SiO(CH_2)_2$		65[e]
p-Cl	*n*-C_5H_{11}		43[e]
p-COOEt	*n*-C_5H_{11}		45[e]
1-naphthol	*n*-C_5H_{11}		78

[a] See text for typical experimental procedures. [b] Isolated yields are shown. Yield of monoalkenylated phenol/dialkenylated phenols are shown when formed. Satisfactory spectroscopic data (^{1}H-NMR, ^{13}C-NMR, IR, and MS) as well as elemental analyses either by HRMS or by combustion were obtained. [c] Molar ratio, phenol:1-alkyne:reagent 1:1.2:3. [d] Isolated as acetate. [e] Molar ratio, phenol:1-alkyne:reagent 1:5:8.

Scheme 1



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(1) For examples of acetylenes: Cook, O. W.; Chambers, V. J. *J. Am. Chem. Soc.* **1921**, *43*, 334. Yuldashev, K. Y.; Tsukervanik, I. P. *J. Gen. Chem. USSR* **1964**, *34*, 2668. Zinov'eva, L. V.; Ryabov, V. D. *J. Org. Chem. USSR* **1984**, *20*, 540. For examples of vinyl halides and triflates: Schmerliong, L.; West, J. P.; Welch, R. W. *J. Chem. Soc.* **1958**, *80*, 576. Yuldashev, K. Y.; Tsukervanik, I. P. *J. Gen. Chem. USSR* **1968**, *32*, 1268. Stang, P. J.; Anderson, A. G. *Tetrahedron Lett.* **1977**, 1485.

(2) In some cases, vinyl halides with stabilizing groups, such as aryl or phenylthio groups were employed in the aromatic alkenylation: Roberts, R. M.; Abdel-Baset, M. B. *J. Org. Chem.* **1976**, *41*, 1698. Stang, P. J.; Anderson, A. G. *J. Am. Chem. Soc.* **1978**, *100*, 1520. Kitamura, T.; Kobayashi, S.; Taniguchi, H.; Rappoport, Z. *J. Org. Chem.* **1982**, *47*, 5003. Takeda, T.; Kanamori, F.; Matsusita, H.; Fujiwara, T. *Tetrahedron Lett.* **1991**, *32*, 6563.

(3) Bader, A. R. *J. Am. Chem. Soc.* **1955**, *77*, 4155.

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(5) Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G.; Terenghi, G. *J. Chem. Res. (S)* **1977**, 96. Casiraghi, G.; Casnati, G.; Sartori, G.; Bolzoni, L. *J. Chem. Soc., Perkin Trans 1* **1979**, 2027.

(6) Corson, B. B.; Heintzelman, W. J.; Schwartzman, L. H.; Tiefenthal, H. E.; Lokken, R. J.; Nickels, J. E.; Atwood, G. R.; Pavlik, F. J. *J. Org. Chem.* **1958**, *23*, 544. Also see references cited therein. Cleavage of benzofuran derivatives was also reported: Gripenberg, J.; Hase, T. *Acta Chem. Scand.* **1966**, *20*, 1561. Oude-Alink, B. A. M.; Chan, A. W. K.; Gutsche, C. D. *J. Org. Chem.* **1973**, *38*, 1993.

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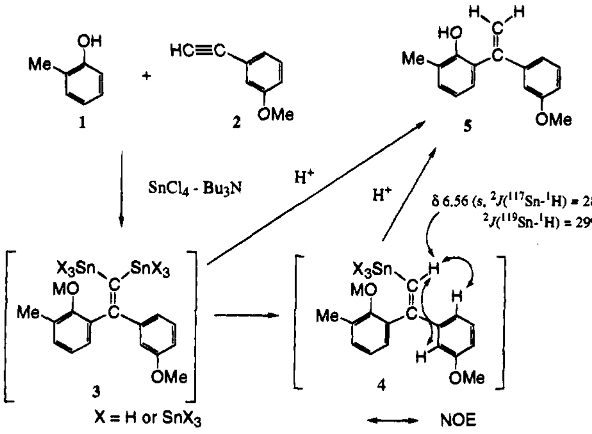
Scheme 2



in acetonitrile. The alkenylation does not proceed with a disubstituted alkyne, 1-phenyl-1-decyne.

The C−C bond formation takes place *via* carbostannylation of trichlorophenoxytins[7] and alkynyltrichlorotins[8] generated *in situ*. Heating a mixture of *o*-cresol (**1**), *m*-methoxyphenylacetylene (**2**), $SnCl_4$, and Et_3N at 80 °C for 10 min in CD_2Cl_2 gave an intermediate **3** as detected by NMR (Scheme 2). **3** did not possess an olefinic proton. When heating was continued for 30 h, **3** was slowly converted to the second intermediate **4**. The structure of **4** was determined as a monostannylalkene, NMR spectra of which showed a vinyl proton accompanied by satellites attributable to $^{117/119}Sn-^{1}H$ couplings. (*Z*)-Stereochemistry was determined by NOE studies. Both **3** and **4** gave the alkenylated phenol **5** in high yields on aqueous workup, indicated that **3** and **4** had the same carbon framework. Thus, **3** was assigned as 1,1-bis(stannyl)alkene. These observations as well as their similarity to the previous reaction[9] support the carbostanylation mechanism.

The regioselective *exo*-olefin formation can be explained on the basis of the electrophilic properties of alkynyltrichlorotins at the β-carbon atom, given the higher reactivities of electron-rich phenols relative to electron-deficient phenols.[10] *Ab initio* calculations[11] of $HC\equiv CSnF_3$ (**6**)[12] show that the β-carbon atom is less negatively charged than the α-carbon atom (Figure 1). In addition, the coefficients of π^* orbitals of C−C triple bond are larger at the β-carbon atom. These tendencies are more prominent with **6** than with $HC\equiv CSnH_3$ (**7**), in keeping with the spectroscopic data and experimental results.[13] The acetylenic β-carbon of alkynyltrichlorotin **8** appears at lower field by ^{13}C-NMR compared with alkyltrialkyltin **9**.[14] The carbostannylation seems to be controlled by the electronic character of these tin reagents, although we have no information on the transition state structure. A different reaction course may be involved in the β-(trimethylsilyl)ethenylation.

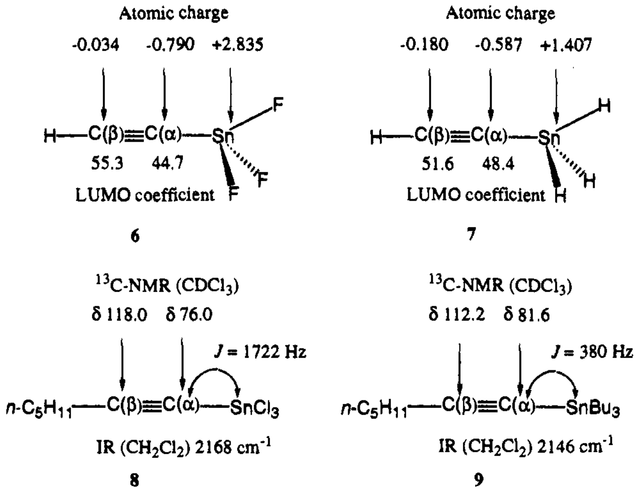


Figure 1.

Experimental procedures are as follows. Under an argon atmosphere, a mixture of *o*-cresol (649 mg, 6.0 mmol), 4-phenyl-1-butyne (651 mg, 5.0 mmol), $SnCl_4$ (1.29 mL, 11.0 mmol), and Bu_3N (2.62 mL, 11.0 mmol) in acetonitrile (20 mL) was refluxed for 7 h, after which the reaction was quenched by addition of 2 M NaOH. After acidification with 2 M HCl, the organic materials were extracted with ether, washed with water and brine, dried over $MgSO_4$, and concentrated *in vacuo*. 6-Methyl-2-(4-phenyl-1-buten-2-yl)phenol (809 mg, 68%) was obtained by flash chromatography (hexane:ethyl acetate 20:1) over silica gel.

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Supplementary Material Available: Procedures of vinylation reaction and β-(trimethylsilyl)ethenylation reaction, spectral data of products, and those of intermediates **3** and **4** (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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[7] Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G.; Terenghi, G. *J. Chem. Soc., Perkin Trans. I* **1980**, 1862.

[8] Yamaguchi, M.; Hayashi, A.; Hirama, M. *Chem. Lett.* **1992**, 2479.

[9] Yamaguchi, M.; Hayashi, A.; Hirama, M. *J. Am. Chem. Soc.* **1993**, *115*, 3362. Hayashi, A.; Yamaguchi, M.; Hirama, M.; Kabuto, C.; Ueno, M. *Chem. Lett.* **1993**, 1881.

[10] It was observed that the alkenylation of *m*-(methoxycarbonyl)phenol was much slower than that of *p*-(ethoxycarbonyl)phenol.

[11] All calculations were carried out at RHF/LANL1MB level by using Gaussian 92. The NBO analyses were made with respect to the fully optimized geometries. We evaluated atomic charges and orbital coefficients on the basis of the NBO analyses. Frisch, M. J.; Trucks,, G. W.; Head-Gordon, M.; Gill, P. M. W.; Wong, M. W.; Foresman, J. B.; Johnson, B. G.; Schlegel, H. B.; Robb, M. A.; Replogle, E. S.; Gomperts, R.; Andres, J. L.; Raghavachari, K.; Binkley, J. S.; Gonzalez, C.; Martin, R. L.; Fox, D. J.; Defrees, D. J.; Baker, J.; Stewart, J. J. P.; Pople, J. A. *Gaussian 92*, Revision A; Gaussian, Inc.: Pittsburgh, PA, 1992.

[12] Calculations with the SnF_3 derivative are not unreasonable, since SnF_4 also promotes the ortho-alkenylation of phenols.

[13] The alkenylation does not take place between $PhC\equiv CSnBu_3$ and $PhOSnBu_3$ in acetonitrile. The low ability of $PhC\equiv CSnBu_3$ to serve as the carbostannylation acceptor compared with $PhC\equiv CSnCl_3$ may be one of the reasons for the inertness. When $SnCl_4$ and Bu_3N were added to this mixture, the alkenylated phenol was obtained in a good yield.

[14] The $SnCl_3$ group polarizes the triple bond by the inductive effects, as shown by the higher wave number of C≡C absorption for **8** than for **9**. The discussions are well established in the case of carbonyl group: Bellamy, L. J. *Advances in Infrared Group Frequencies*; Methuen & Co. Ltd.: Suffolk, 1968; p 135. Also see: Nakanishi, K. *Infrared Absorption Spectroscopy*; Holden-Day, Inc.: San Francisco and Nankodo Co. Ltd.: Tokyo, 1962; Chapter 3.