REGIOSELECTIVE PRENYLATION OF PHENOLS BY PALLADIUM CATALYST: SYNTHESES OF PRENYLPHENOLS AND CHROMANS

Masao Tsukayama,* Makoto Kikuchi, and Yasuhiko Kawamura

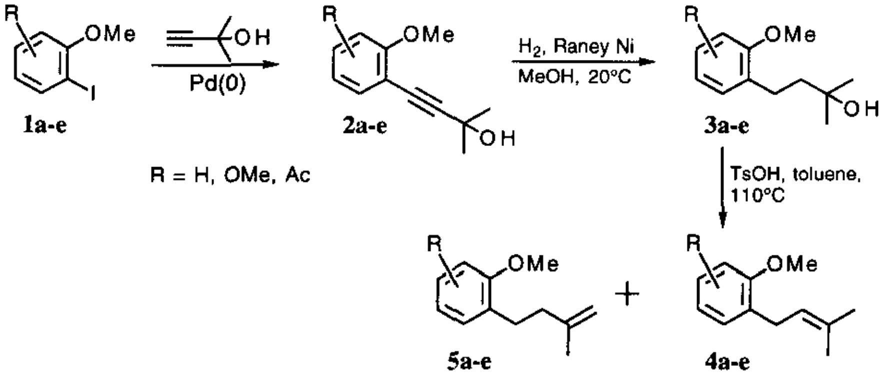
Department of Chemical Science and Technology, Faculty of Engineering,
The University of Tokushima, Minamijosanjima-cho, Tokushima 770, Japan

Abstract –The palladium-catalyzed coupling reaction of iodophenols (**1**) with 2-methyl-3-butyn-2-ol gave alkynylphenols (**2**). Catalytic hydrogenation of **2** over Raney nickel and the subsequent dehydration of the resultant alkylphenols (**3**) gave regioselectively the desired prenylphenols (**4**). Dehydration of alkylphenols (**3f-h**) gave chromans (**7**).

Prenylphenols are potentially valuable intermediates in the synthesis of chromenes, chromans, and natural products[1] and distributed widely in nature.[2] These compounds are also useful model compounds for biogenetic studies[3] and have antifungal activity.[4] Although these compounds have been synthesized from suitable phenols by direct acid- or based-catalyzed alkylation, or by Claisen rearrangement,[5] the majority of such reactions has resulted in relatively far from satisfactory yields. The Friedel-Crafts reactions of phenols bearing strongly electron-withdrawing substituents with allyl chloride have not entirely reacted.[6]

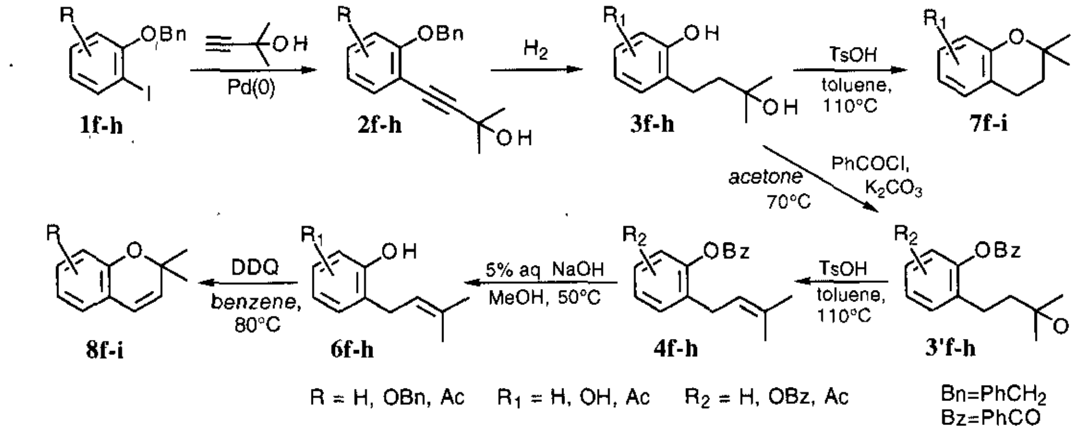
The reaction of aryl halides with terminal alkynes in the presence of Pd(0) is very useful for the formation of carbon-carbon bonds.[7] We report here the first regioselective synthesis of prenylphenols by using the palladium-catalyzed coupling reaction of iodophenols with 2-methyl-3-butyn-2-ol and synthesis of chromans.

Iodophenols were synthesized from the corresponding phenols with iodine in the presence of silver

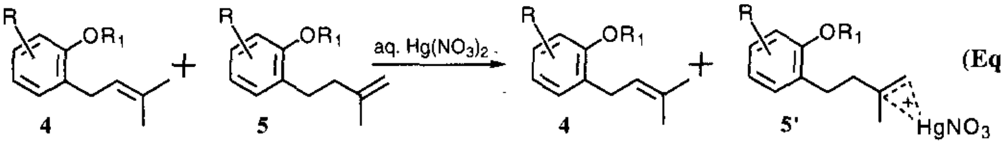


Scheme 1

trifluoroacetate in $CHCl_3$ at room temperature. 4'-Hydroxy-3'-iodoacetophenone was synthesized by NaI-NaClO method.[8] The coupling reaction of the phenols (**1**) (1 mmol) with 2-methyl-3-butyn-2-ol (3 mmol) in the presence of $PdCl_2$ (0.03 mmol), CuI (0.03mmol), and PPh_3 (0.06 mmol) in Et_3N—DMF under N_2 under suitable conditions afforded the desired alkynylphenols (**2**) in high yields (Schemes 1 and 2, Table 1). However, the coupling reaction of **1c** gave alkynylphenol (**2c**) in a lower yield than those of other compounds because of the steric hindrance and the electron-releasing groups, whereas the coupling reaction of acetophenones (**1d**,**e**,**g**,**h**) gave the alkynylphenols (**2d**,**e**,**g**,**h**) in high yields because of the strongly electron-withdrawing group. After catalytic hydrogenation (Raney Ni) of alkynylphenols (**2**), the obtained alkylphenols (**3a-e**, **3'f-h**) were dehydrated with $TsOH{\cdot}H_2O$ under reflux in toluene 0.5-1.5 h to give a mixture of the desired prenylphenols (**4**) and a small amount of the isomers (3-methyl-3-butenylphenols) (**5**) in high yields. It is difficult to separate **4** from the mixtures by column chromatography or distillation. The mixtures were treated with aq. $Hg(NO_3)_2$ (1.3 equiv. based on the isomers) in tetrahydrofuran at room temperature for 0.5 h to give the terminal alkylmercurinium ions (**5'**) by equation 1,[9] and then the desired prenylphenols (**4**) were easily separated and purified from the mixtures by silica gel column chromatography ($CHCl_3$ as solvent) (Table 1). In the reaction of the alkene mixtures with $Hg(NO_3)_2$, the internal alkylmercurinium ions were not obtained. This separation procedure is the first attempt to separate the desired prenylphenols from the mixtures of the internal and terminal alkenes The reaction of $Hg(NO_3)_2$ to only terminal alkenes may be used as a convenient test for terminal alkenes, as well as a method for separation of a mixture of internal and terminal alkenes. Benzoyloxyprenylphenols (**4f-h**) were also purified by the same method. Hydroxyalkylphenols (**3f-h**) were converted into chromans[10] (**7f-h**) with $TsOH{\cdot}H_2O$ in high yields. Benzoyloxyprenylphenols (**4f-h**) were hydrolyzed to hydroxyprenylphenols[10] (**6f-h**), and then were subsequently converted into chromenes (**8f-h**) with DDQ in benzene The coupling reaction of 2-tosyloxybromobenzene (**1i**) having the electron-withdrawing-

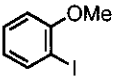
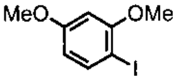
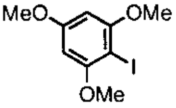
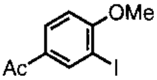
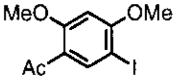
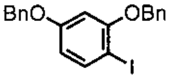
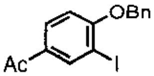
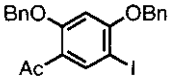
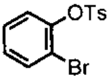


Scheme 2



(Eq. 1)

Table 1. Synthesis of Alkynylphenols and Prenylphenols[a)]

Phenol	React. cond.	Alkynylphenol (Yield %)	Alkene mixture (Yield %) (A/B)[b)]	Prenylphenol[c)] (Yield %)
 **1a**	50°C, 0.5 h	**2a** 97 Paste	93 (87/13)	**4a** 80 Oil
 **1b**	50°C, 0.5 h	**2b** 90 Paste	95 (91/9)	**4b** 85 Oil
 **1c**	80°C, 21 h	**2c** 67 Oil	90 (85/15)	**4c** 75 Oil
 **1d**	25°C, 5 h	**2d** 87 mp 97-98°C	94 (90/10)	**4d** 83 Oil
 **1e**	85°C, 0.5 h	**2e** 90 mp 125-126°C	93 (89/11)	**4e** 81 mp 52-54°C
 **1f**	80°C, 2 h	**2f** 71 mp 90-92°C	96 (87/13)	**4f** 82 Oil
 **1g**	85°C, 1 h	**2g** 84 mp 105-107°C	85 (88/12)	**4g** 73 Oil
 **1h**	70°C, 2 h	**2h** 95 mp 122-124°C	96 (87/13)	**4h** 82 Oil
 **1i**	80°C, 8 h	**2i** 70 Oil	88 (87/13)	**4i** 75 Oil

a) Yields isolated by column chromatography are given. Identification of all the products was achieved by ^{1}H-nmr evidence and elemental analysis.

b) Mixture of two isomers A=prenylphenol (**4**) and B=3-methyl-3-butenylphenol (**5**); A/B=proportion of isomers was determined by ^{1}H-nmr.

c) Isolated yields based on the corresponding alkylphenols (**3a-e** and **3'f-h**).

group also gave easily alkynylphenol (**2i**), and then converted into prenylphenols (**4i** and **6i**[10]), chroman[10] (**7i**) and chromene (**8i**). In conclusion, the palladium-catalyzed coupling reaction of iodophenols with 2-methyl-3-butyn-2-ol has shown to be a useful method for regioselective syntheses of prenylphenols bearing strongly electron-withdrawing substituents and chromans. The excellent chemoselectivity of $Hg(NO_3)_2$ to internal and terminal alkenes has been shown to be useful for the recognition and separation of terminal alkenes.

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10. 4-(3-Methyl-2-butenyl)resorcinol (**6f**), mp 63-65 °C, colorless needles (hexane-CCl_4); 4'-hydroxy-3'-(3-methyl-2-butenyl)acetophenone (**6g**), mp 92-93 °C, colorless needles (hexane-ether); 4',6'-dihydroxy-3'-(3-methyl-2-butenyl)acetophenone (**6h**), mp 139-141 °C, colorless needles (hexane-ether); 2-(3-methyl-2-butenyl)phenol (**6i**), colorless oil.
    Chromans: **7f**, oil (82% yield); **7g**, mp 92-94 °C (87% yield), colorless needles (hexane-ether); **7h**, mp 116-118 °C (85% yield), colorless needles (hexane-ether); **7i**, oil (85% yield).

Received, 14th March, 1994